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SOME SURGICAL ASPECTS OF THE MALABSORPTION SYNDROME*

BY

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The nutritional status of man depends on an adequate intake of food followed by its efficient digestion and absorption from the intestine. While numerous factors within the intestinal lumen, such as *p*H, motility, mucosal surface, bacteria, secretory hormones, and certain disease states, are known to influence absorption from the intestine, the precise processes whereby the nutritional products of digestion are absorbed into the blood-stream to be transported to the metabolic pools of the body remain obscure.

The malabsorption syndrome presents a challenge to those concerned in its treatment, and poses many problems which have stimulated research in many different fields. Thus the physiologist is attracted by the evidence of abnormal gastro-intestinal function; the haematologist by changes in absorption of vitamin B_{12}, folic acid, and iron; the nutritionist by the discovery that dietary factors may play a part in aetiology; the biochemist by the possibility of alterations in the metabolism of calcium, potassium, and lipids; and the bacteriologist by the unresolved enigma of the intestinal flora. For these reasons the malabsorption syndrome provides a common meeting-ground for workers in a number of different disciplines. The surgeon has an important part to play in this co-operative research. By his manipulations and resections of the small intestine he may inadvertently produce the syndrome; by further surgery he can sometimes effect its cure; by virtue of his scientific training — and this can be his greatest contribution—he has a unique opportunity to glean vital information from these surgical experiments.

Of the many aspects of the malabsorption state which interest surgeons, I have elected to consider some causes directly attributable to operative alteration of the continuity, motility, or digestive secretions of the gastro-intestinal tract. Malabsorption due to gastrectomy, vagotomy, "culs-de-sac," gastro-colic fistula, and massive resection of the small intestine is discussed with special reference to the mechanisms responsible for gastro-intestinal dysfunction.

Malabsorption after Gastrectomy

Impaired nutrition after gastrectomy is commonly the result of reduced intake of food. In some patients, however, malabsorption plays an important part, and may lead to severe loss of weight, steatorrhoea, and even vitamin deficiencies (Anderson *et al.*, 1955).

Reduced intake is an important cause of impaired nutrition after gastrectomy in patients who are aware of a feeling of fullness and discomfort after meals and who consequently tend to limit the size of their meals. It would seem a simple matter to encourage such patients to increase their intake of food, but, unfortunately, when the loss of food in the faeces is greatest the capacity for food is often smallest. The best advice for this group of patients is to encourage them to take frequent small meals. In severe cases, jejunal or colonic replacement procedures, by providing a food reservoir, are rational and are worthy of consideration.

Impaired absorption of food after gastrectomy may be due to any one or to any combination of the following factors.

Possible Causes of Post-gastrectomy Malabsorption

1. Rapid gastric emptying and intestinal passage of food.
2. Impaired pancreatic-biliary digestion from:
   (*a*) Inadequate mixing of food with secretions.
   (*b*) Inadequate production of secretions.
3. Activation of latent steatorrhoea.
4. Afferent loop (Polya) acting as cul-de-sac.
5. Bacterial colonization of jejunum.

Rapid gastric emptying and intestinal passage of food, more pronounced after Polya than after Billroth I gastrectomy (Meurling, 1953), predispose to malabsorption by reducing the contact time between intestinal contents and absorbing surface. The more normal pattern of emptying from the stomach and upper intestine in Billroth I patients has been neatly confirmed by adding radio-iodinated human serum albumin to a test meal and employing the technique of "external counting" (Lundh, 1957). After total gastrectomy there is an extremely rapid intestinal passage of the meal.

The hormones secretin and pancreozymin, liberated into the blood-stream by the action of gastric hydrochloric acid on the duodenal mucosa, stimulate the secretion of pancreatic juice and provoke contraction of the gall-bladder. These mechanisms, essential for normal digestion, may be deranged in one of the following ways after gastrectomy.

Firstly, in Polya gastrectomy (gastro-jejunal anastomosis) food precedes the bile and pancreatic secretions down the small intestine, instead of meeting and merging with it. It is not surprising, therefore, that the faecal excretion of fat is usually greater after Polya than after Billroth I gastrectomy—gastro-duodenal anastomosis (Wollaeger, 1950). When this factor is judged to be of major importance in the production of steatorrhoea a conversion operation (Polya to Billroth I) is indicated. Secondly, the secretin and pancreozymin mechanisms are inactivated in patients who fail to secrete acid after gastrectomy, and malabsorption may follow. Attempts to remedy this defect by the administration of dilute hydrochloric acid or by pancreatic enzyme

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substitution therapy have yielded very variable results; some of the failures may be explained on the basis of inadequate dosage. Finally, while many patients continue to secrete appreciable amounts of acid after partial gastrectomy, this stimulus for the release of secretin and pancreozymin can be effective only after gastro-duodenal anastomosis; a gastro-jejunal anastomosis permits the acid to escape directly into the jejunum. A conversion from Polya to Billroth I may be beneficial in selected cases.

Paulley and his colleagues (1957) postulate that severe steatorrhoea and loss of weight after gastrectomy may be due to aggravation of a latent idiopathic steatorrhoea. They have gained support for this hypothesis by showing a correlation between the state of the jejunal mucosa (biopsied at the time of gastrectomy) and the patient's subsequent progress, and conclude that jejunal biopsy may prove a useful screening measure before gastrectomy.

It has been suggested that the afferent loop of a Polya gastrectomy may cause malabsorption by acting as a cul-de-sac. However, this particular loop of intestine is exceedingly active, empties itself readily (regularly observed on screening after a barium meal), and is normally washed through by bile and pancreatic juice after each meal. Thus it does not permit the stagnation of intestinal content which is critical for the development of a "cul-de-sac" syndrome (see below).

Finally, it has been suggested that the vitamin-B deficiencies which occasionally follow gastrectomy are due to colonization of the jejunum by organisms from the lower bowel which compete with the host for the vitamins (Welbourn *et al.*, 1951). However, while *Cl. welchii* are often present in large numbers in the contents of the gastric remnant during the first week after gastrectomy, a study of specimens of jejunal content from post-gastrectomy patients with loss of weight and anaemia showed no evidence of continued colonization of the upper small intestine (Duncan *et al.*, 1954).

Malabsorption after Vagotomy

Vagotomy as a sole therapeutic procedure is followed by troublesome symptoms (distension, foul eructations, nausea, vomiting, and diarrhoea) which are largely preventable by the addition of a drainage operation such as gastro-jejunostomy or pyloroplasty. Diarrhoea after either of these procedures (emphasized as a frequent and serious disadvantage by surgeons who prefer gastrectomy) is not, in my experience, a common or troublesome complication. In a follow-up study of 661 consecutive vagotomy and gastro-enterostomy operations, Feggetter (1959) found 28 patients who complained of diarrhoea, an incidence of 4.3%. In most cases the alteration in bowel habit is a welcome correction of the constipation commonly associated with ulcer dyspepsia; in some there may be a history of several loose stools in the morning; in a few the diarrhoea is associated with intestinal malabsorption. In this last group the impaired absorption of food may be due to one or more factors.

Though the secretin and pancreozymin mechanisms are unlikely to be disturbed greatly by the drop in gastric acid secretion which follows vagotomy, these may be nullified when the available acid by-passes the duodenum through a gastro-jejunostomy; this is a reason for preferring pyloroplasty to gastro-jejunostomy as the drainage procedure.

On the basis that the diarrhoea is due to loss of the nervous component of pancreatic secretion consequent on division of the pancreatic branches of the vagus, Burge and Clark (1959) have developed the operation of selective vagotomy with preservation of the coeliac division of the posterior nerve. This ingenious operation merits controlled comparison with standard vagotomy in relation to the incidence of diarrhoea and of recurrent peptic ulceration. The aim of vagal section in the treatment of duodenal ulcer is to reduce the secretion of hydrochloric acid, and selective vagotomy will not supplant complete vagotomy unless it can be shown to be equally effective in this respect.

Post-vagotomy diarrhoea has been attributed by some to stasis and by others to intestinal hyperactivity (Fox and Grimson, 1950). Apparently irreconcilable, either may predominate in the individual case. It is difficult to predict the net effect upon motility of interrupting the vagal pathways, and familiarity with this procedure has taught us that the function of the extrinsic nerves is not to supply the gut with motor power from without but rather to adapt the motility inherent in the bowel to conditions and needs in other parts of the organism.

"Cul-de-sac" Syndrome

That ulcerating lesions of the small intestine may bleed and give rise to microcytic anaemia has been fully appreciated by surgeons for many years. Renewed interest in the small bowel has followed the demonstration that macrocytic anaemia and steatorrhoea may occasionally follow operations which result in the formation of by-passed loops or culs-de-sac in which intestinal contents can stagnate (Watson and Witts, 1952). This symptom-complex has also been reported in a number of diverse intestinal abnormalities, including intestinal stricture and massive diverticulosis. The cul-de-sac syndrome involves two groups of symptoms: firstly, intestinal dysfunction results in malnutrition, steatorrhoea, macrocytic anaemia, and vitamin deficiencies; and, secondly, the anatomical abnormality may cause symptoms of recurring intestinal obstruction.

The malabsorption is probably the result of an altered bacterial flora in the intestine which is apt to occur only when the arrangement of the cul-de-sac permits stagnation of its contents. Thus Cameron *et al.* (1949) found that blind loops fashioned to ensure ready emptying had no effect on the nutrition of rats; when the loops were arranged so that they filled but had difficulty in emptying, weakness, loss of weight, and steatorrhoea occurred. Unless these rather critical conditions are fulfilled, an intestinal abnormality will not cause malabsorption.

Normally, certain bacteria in the intestine are capable of synthesizing various essential food factors, including the B-vitamins. When stagnation occurs in a blind loop it seems that other bacteria proliferate, reduce the population of synthesizing organisms, and acquire for their own use the essential food factors required by the host (Fig. 1). This hypothesis is supported by the ability of some antibiotics to reverse this process and give clinical improvement with correction of both the steatorrhoea and the macrocytic anaemia.

The association of macrocytic anaemia, steatorrhoea, and abdominal cramps in a patient who has had a previous operation should make the clinician consider a diagnosis of cul-de-sac syndrome; a good clinical

response to an antibiotic is strong evidence in support of this diagnosis (Fig. 2).

Given a reliable diagnosis, the cul-de-sac syndrome can be cured in the majority of patients by resection of the blind loop or diverticulum. The surgeon is faced with a more difficult problem if the bowel is the seat of massive diverticulosis; resection under these circumstances may perpetuate intestinal insufficiency by removing a critical length of small intestine.

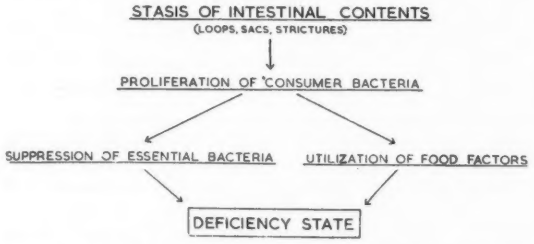

FIG. 1.—Probable sequence of events resulting in a deficiency state in cul-de-sac syndrome.

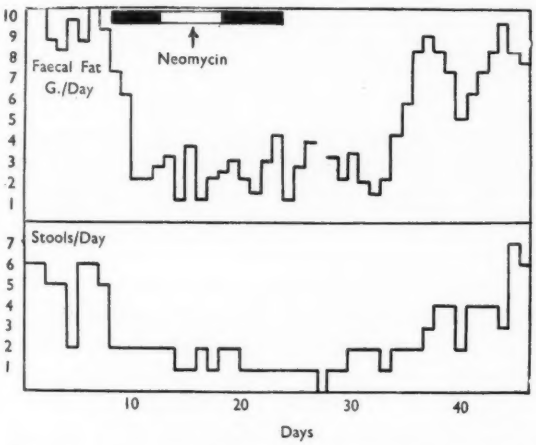

FIG. 2.—Improvement in steatorrhoea during treatment with neomycin in a patient with cul-de-sac syndrome (50 g. fat per day) due to previous entero-enterostomy for acute small-bowel obstruction.

The dangers of producing stagnant loops of intestine are now widely recognized, and it is likely that fewer cases of the cul-de-sac syndrome will occur. Surgeons are aware of the dangers of short-circuit operations, and prefer end-to-end anastomosis to side-to-side anastomosis. In the past, by innocently creating this malabsorption picture, they have provided opportunity for profitable studies on the pathogenesis of the megaloblastic anaemias and on the biosynthesis of vitamins in man.

Gastro-colic Fistula

Gastro-colic fistula, with its dramatic nutritional disturbances, may be regarded as a severe form of cul-de-sac syndrome. In a series of cases of gastro-colic fistula reviewed at the Mayo Clinic, 50% of patients were noted to have clinical evidence of avitaminosis (Atwater *et al.*, 1943). The condition occurs as a complication of gastro-jejunal ulceration or, rarely, from cancerous invasion between the stomach and colon. The belief that malabsorption follows loss of gastric contents directly into the colon has now been clearly disproved; the concept that diarrhoea results from the introduction of colonic bacteria into the proximal jejunum has been substantiated by the relief afforded regularly by proximal colostomy and by the benefit which follows treatment with intestinal antibiotics—now one of the mainstays of pre-operative preparation.

Though successful closure of the fistula will cure the malabsorption state, the safe management of these patients depends on an intelligent appreciation of the inherent biochemical problems. Relatively simple biochemical techniques can be used to demonstrate the profound alteration in electrolyte and nutritional balance which may result from a fistula and to monitor the rapid improvement on adequate preoperative therapy; a synopsis of one of my own cases, previously reported in detail by Connell (1957), is illustrative.

A man aged 32 was admitted to hospital complaining of severe and malodorous diarrhoea, foul eructations, extreme loss of weight, abdominal distension, and loss of energy. He gave a history of gastro-jejunostomy done for pyloric stenosis seven years previously. A reduction in the plasma proteins to 50% of normal was consistent with the gross oedema and ascites; the results of thiamine and riboflavine saturation tests were in keeping with the observed clinical signs of vitamin-B deficiency—pellagra and angular stomatitis; a serum calcium level of 6.9 mg./100 ml. explained the marked motor hyperexcitability and positive Chvostek sign; a greatly reduced serum potassium level may have accounted for his mental aberrations and extreme lassitude. Pre-operative treatment with a high-protein diet, 1 pint (570 ml.) of plasma intravenously every alternate day, and intramuscular vitamin-B complex, together with control of his diarrhoea by means of hexamethonium and chlortetracycline, resulted in a return of the abnormal biochemical findings to normal before operation. Operation, in a now fit subject, presented no difficulty, and within one month of discharge from hospital the patient had gained 1½ stone (9.5 kg.) in weight and had already returned to full work. Three years after operation he was still symptom-free.

Massive Resection of the Small Intestine

The clinical and metabolic effects of massive intestinal resections are of practical importance now that the surgeon, confident in the reliability of supportive measures and the high standard of modern anaesthesia, is able to remove large segments of diseased gut. Fortunately, the surgeon to-day is interested in the study of such cases and so has been able to advance our understanding of the physiology of the small intestine. This attitude of surgeons will be greatly appreciated by their patients, who are likely to be more interested in their own nutritional status than in the technical achievement of resecting a record length of gut.

While resection of up to two-thirds of the small bowel is compatible with good health, resections of greater extent will almost certainly result in malabsorption; when less than 18 in. (46 cm.) of small intestine remains after resection, death from inanition is likely. This knowledge is of practical importance when the surgeon encounters multiple segments of Crohn's disease and has to choose between an extensive resection or the making of several entero-anastomoses, with the inherent dangers of blind loops.

The patient who recovers from a massive resection has to face a period of post-operative fluid and electrolyte loss from profuse diarrhoea, which may persist for two to three weeks. When this crisis has passed the emphasis shifts from fluid imbalance to nutritional disturbance. Despite an adequate food intake, the

passage of bulky fat-laden stools leads to rapid loss of weight. The absorption of protein and of carbohydrate is also impaired, but to lesser degree than that of fat. In the absence of treatment, vitamin deficiencies, hypocalcaemia, hypoproteinaemia, and anaemia may occur. Gradually, compensatory mechanisms assert themselves and halt this progressive starvation. The lowered body weight permits survival on reduced calorie requirements and reduces the demand for protein replacement: anatomical adaptation involving hypertrophy of the remaining small intestine and its mucosal villi augments absorption; the colon increases its ability to absorb water, amino-acids, and crystalloids; reduction in the rate of gastric emptying allows an increased time for contact between food and mucosal surface. This last form of adaptation is well illustrated by the following case-history.

In a man aged 40, massive intestinal strangulation in an internal hernia necessitated resection of the caecum and of the small bowel to within 3 ft. (91 cm.) of the duodenojejunal flexure. He developed the typical starvation-steatorrhoea syndrome. Six months after operation he noticed a sudden and striking improvement in his symptoms coincident with the onset of epigastric discomfort and occasional vomiting of retention type. He gave a previous history of duodenal ulceration and a clinical and radiological diagnosis of pyloric stenosis was made. The addition of a gastro-jejunostomy in this particular patient was clearly undesirable, and he was trained to perform nightly gastric lavage with half-strength saline; on this regime he continued in good health for about eight years. It is highly probable that the pyloric obstruction had improved intestinal absorption by promoting "drip feeding" from the stomach into the residual small intestine. An operation planned to produce a degree of pyloric obstruction in patients with insufficient small intestine is rational and worthy of further study.

Repeated haematological studies in patients having had extensive resection of the distal small bowel may shed light on the disputed site of absorption of vitamin B_{12}. Recent experimental work in the rat suggests that the ileum is the chief site of absorption of this vitamin and that resection of this part of the gut predisposes to macrocytic anaemia (Booth *et al.*, 1957). The patient whose history is described above had a mild microcytic anaemia, but repeated examination of the peripheral blood and bone-marrow has not revealed any sign of a developing macrocytic anaemia; the entire distal small bowel was removed, and yet, almost nine years later, there is no evidence of vitamin-B_{12} deficiency, and tests have shown satisfactory vitamin-B_{12} absorption (intestinal continuity was restored by anastomosing the jejunum to the ascending colon). This may reflect either a species difference or the ability of the jejunum to assume the function of absorbing this vitamin.

Conclusion

While there has been substantial progress in our understanding of the physiology of the small intestine, our knowledge must still be regarded as rudimentary. However, cases showing varying degrees of malabsorption are by no means uncommon and an increasing number of research tools are becoming available for use in their study. The radioactive labelling of such food factors as vitamin B_{12}, iron, and fats, has already led to a fuller understanding of the absorption of these substances from the intestine. Biopsy of the small intestine (Shiner, 1956) permits a histological study of the mucosal pattern in various disease states; if it is employed before, during, and after specific therapy much new information should be gained. This technique also provides adequate tissue for histochemical and electron-microscopical studies. A readily ingestible pill has now been devised which contains a small radio transmitter, capable of transmitting information about hydrogen-ion concentration, pressure, and temperature during its passage through the small intestine (MacKay and Jacobson, 1958). The challenge is clear; new techniques are available, and intensive study should result in significant progress.

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POST-PUBERTAL ADRENAL VIRILISM WITH BIOCHEMICAL DISTURBANCE OF THE CONGENITAL TYPE OF ADRENAL HYPERPLASIA

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That the adrenal cortex could be the seat of lesions resulting in virilizing changes was first established by Bulloch and Sequeira (1905); the cases with which they were concerned were prepubertal. In 1910 Apert reviewed the available material, and developed a classification involving all age-groups which is the basis of that in use to-day. He was responsible for the present term "adrenal virilism," while the term "adreno-genital syndrome" derives from Gallais (1912). The syndrome was intensively studied by Broster and Vines (1933) prior to the second world war. It is apparent that the terminology used in the classification of these conditions has become confused. Thus the term "adreno-genital syndrome" may include cases of virilism arising before or after puberty and cases of the Cushing type (Broster, 1953). On the other hand, Wilkins (1957) properly makes a sharp distinction between the adreno-genital syndrome and Cushing's syndrome, including them under the term "hyperadrenocorticism."

Though similar clinical changes may be brought about by adrenal cortical tumours or adrenal cortical "hyperplasia" the present paper is restricted to a

discussion of those patients afflicted with the latter lesion. Adrenal virilism, adreno-genital syndrome, congenital pseudohermaphroditism, congenital adrenal hyperplasia, and hyperadrenocorticism have all been used to describe the same condition. Clearly the term "congenital (female) pseudohermaphroditism" should not be used in this restricted sense, since the clinical condition may be due to other causes (Wilkins, 1957).

As a better understanding of the chemical pathology of the adrenal cortex is gradually being gained, the time has come to urge precision in the nomenclature of these conditions. The following clinical classification will be used as a basis for discussion in the present paper.

ADRENO-GENITAL SYNDROME:

1. *Congenital adrenal hyperplasia* (female pseudohermaphroditism or male precocious puberty due to adrenal cortical hyperplasia).

2. *Post-natal adrenal virilism:* (*a*) Arising prepubertally. (*b*) Arising post-pubertally.

(The adrenals in these patients are often, but not necessarily, enlarged.)

Intensive biochemical studies of a large number of patients of the first group have been made, and it is generally accepted that the ability of the adrenal to synthesize cortisol normally is impaired. This is due to deficiency of 21- or 11-hydroxylation of the steroid nucleus, and results in the excretion of metabolites of accumulated 21-carbon intermediates, such as pregnanetriol and excess of 17-ketosteroids, including metabolites of androgens (Eberlein and Bongiovanni, 1955; Dorfman and Shipley, 1956; Bush *et al.*, 1957; Wilkins, 1957). These biochemical lesions are apparently inborn errors of metabolism and are thought to be inherited as recessive characters (Wilkins, 1957).

By contrast much less is known of the biochemistry of post-pubertal adrenal virilism. To begin with, there is a difference of opinion about the duration of the lesion. Wilkins (1957) implies that an isolated patient developing symptoms at the age of 5 years had a congenital lesion, and makes a similar implication with regard to a patient who reached puberty before she had become markedly virilized (Blizzard and Wilkins, 1957). Greenblatt (1958) is of the opinion that the congenital condition may be latent and have an onset even after puberty. But Dorfman and Shipley (1956) speak of the lesion as being one of "acquired hyperplasia," and Epstein and Kupperman (1959) distinguished a "post-pubertal adreno-genital syndrome" of a different type. Their patients had a late onset and lacked evidence of increased pregnanetriol excretion.

It has been shown that post-pubertal adrenal virilism may be difficult to distinguish by superficial biochemical methods from "simple hirsutism" and indeed from patients with the Stein–Leventhal syndrome. Patients with hirsutism developing post-pubertally showed a continuous spectrum of 17-ketosteroid excretion from normal to moderately high levels (Prunty *et al.*, 1958); out of a series of 32 patients with hirsutism, one was definitely distinguished by the excretion of excessive amounts of pregnanetriol in the urine. Since that time two further cases of a similar nature have been observed, and they are presented here (Cases 2 and 3). Observations on the case previously briefly mentioned are more fully reported here for completeness (Case 1).

Biochemical Methods.—Urinary 17-ketosteroids and 17-ketogenic steroids were determined by methods described in Prunty *et al.* (1959). Pregnanetriol was determined by a slight modification of the method of Bongiovanni and Clayton (1954). Urine tetrahydrocortisone, tetrahydrocortisol, and 11-oxo-pregnanetriol were determined by chromatographic techniques (Brooks and Prunty, 1960).

Case 1

A girl aged 18 presented with severe hirsutism. This began at the age of 14 and included the face particularly, arms, legs, areolae, and linea alba. Menstruation started at the age of 10 and continued in a regular 21-day cycle of three to four days' duration. Temperature records indicated the periods were ovulatory. The clitoris was moderately enlarged and the mammae were small. She was short in stature—5 ft. 2 in. (157.5 cm.)—not obese, but very broad-shouldered (Fig. 1). There was a moderate degree of acne

FIG. 1.—Case 1. Before treatment. Note broad shoulders, small mammae, and short stature.

on her face and on the upper part of her back and shoulders. Vaginal examination indicated that the uterus and ovaries were of normal size, and endometrial biopsy showed the development of a late secretory endometrium. Mentally she was suffering from considerable tension with hysterical episodes.

The urinary steroid investigations are indicated in Table I. She was treated for eight months with a combination of 10 mg. of prednisone and 0.2 mg. of ethinyl oestradiol daily. (The latter was given in a cyclical fashion for three weeks in every four.) This produced definite improvement

TABLE I.—*Urinary Steroid Excretion in mg. Per Day*

	Case 1	Case 2	Case 3
17-Ketosteroid	14·8–20·8	27·8–29·4	14·2–17·5
17-Ketogenic steroid	10·6–19·0	10·6–12·2	9·2–19·3
Pregnanetriol	11·7	7·7	3·7
11-Oxo-pregnanetriol	0·9	—	1·0
Tetrahydrocortisone plus tetrahydrocortisol	0·7	—	1·2
After corticotrophin*:			
17-Ketosteroid	38	29	28
17-Ketogenic steroid	48	25	45
Pregnanetriol	54	15	21

* Third day; 20 units in gelatin intramuscularly twice daily.

in the hirsutism. Whereas she had shaved at least once daily and sometimes twice, it was barely necessary to do so once. The acne greatly improved. Her periods continued regularly. The effect of treatment on the urine steroids is shown in Fig. 2. She then refused treatment for 11 months and the hirsutism relapsed. But on returning to 10 mg. of prednisone with 0.02 mg. of ethinyl oestradiol there was again similar improvement. In addition to reduced growth, the hair became much softer.

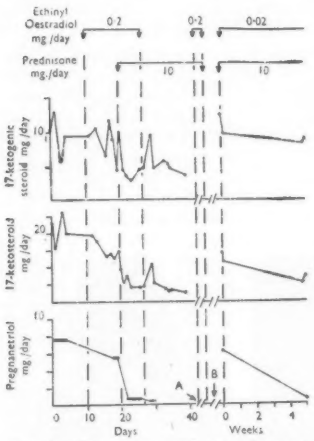

FIG. 2.—Treatment and steroid excretion of Case 1. Steroid excretions are recorded in mg./day. Horizontal bars for pregnanetriol values represent pooled specimens of urine. The break A indicates an eight-months period during which 10 mg. of prednisone and 0.2 mg. of ethinyl oestradiol were given. The break B represents an 11-months period during which no treatment was given.

Case 2

This girl was also aged 18 and had been hirsute for only four years. She had a hairy elder sister. There was a similar distribution of hair growth to that in Case 1, but the condition was much milder. She was 5 ft. 6 in. (167.5 cm.) tall, the breasts were small, shoulders normal (Fig. 3), and the size of the clitoris was probably within normal limits. Periods were regular, but she had not become pregnant after six months of regular intercourse. *X*-ray examination after pelvic insufflation of air showed probable ovarian enlargement. Steroid results are shown in Table I. She was treated with 10 mg. of prednisone daily, which was sufficient to cause marked depression of 17-ketosteroids (Table II), but after 13 months the effects on the hirsutism were minimal. Temperature records before and after treatment suggested ovulation was normal.

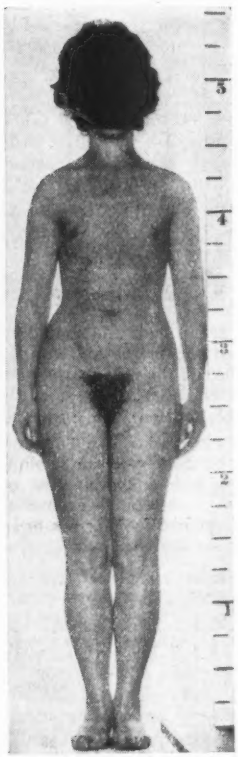

FIG. 3.—Case 2. This patient was much less severely affected than Cases 1 and 3.

Case 3

This girl was aged 20 and presented with very severe facial acne of six years' duration. This was followed by the development of severe facial hirsutism and also involved her body as in Case 1. She had two sisters who were not hirsute. She was 5 ft. 4 in. (162.5 cm.), had moderately small mammae, and the clitoris was definitely enlarged. She, too, was broad-shouldered (Fig. 4). Menstruation began at age 12, then stopped for six months. Finally, it became irregular, occurring at intervals of two to three months. The acne was very severe and produced scarring of her face and over her shoulders.

TABLE II.—*Urine Steroid Response to Steroid Therapy*

	Prednisone Dose (mg. Day)	Duration (Months)	Urine (mg. Day)		
			17-Keto-steroid	17-Ketogenic Steroid	Pregnan-etriol
Case 2 . .	10	4	5·9	7·0	1·3
		13	3·6	10·9	—
Case 3 . .	20	1	5·5	16·3	—
	15	2	8·3	14·3	—
		6	10·3	12·2	—
	20	1½	3·0	11·8	—
	15	1	5·4	13·8	—

She was treated with 15 or 20 mg. of prednisone daily for 14 months (Table II). The larger dose was used partly on account of the severity of her condition and partly because there was some evidence that 15 mg./day was insufficient to cause adequate suppression of 17-ketosteroids. The treatment produced a dramatic and sustained effect on the acne, but much less effect on the hirsutism (Fig. 4). Periods became regular at 4-weeks intervals. The relatively large dose of prednisolone produced mooning of the face.

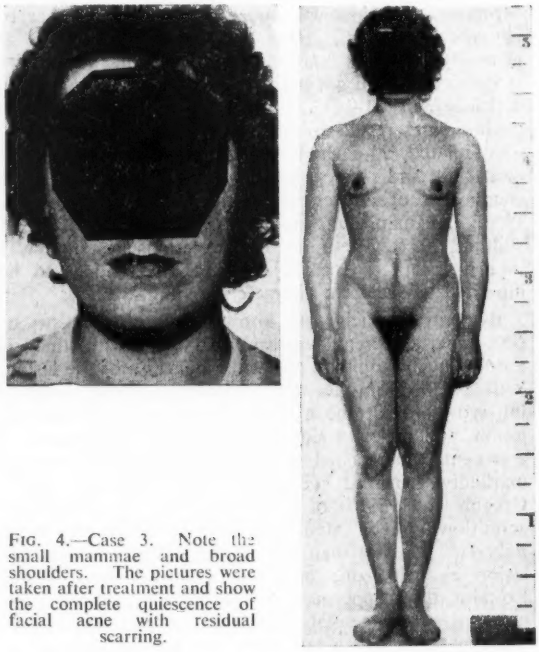

FIG. 4.—Case 3. Note the small mammae and broad shoulders. The pictures were taken after treatment and show the complete quiescence of facial acne with residual scarring.

Discussion

These three patients all developed hirsutism, and two of them acne, *after* normal menstruation had been established. All had poor mammary development, two clitoral enlargement, and two normal ovulatory periods. One patient was noticeably short and two were broad-shouldered. None had hypertension. The family history varied; one patient had no sisters and there was no history of hirsutism in the family; a second (Case 2) had a hairy sister, but unfortunately it was impossible to obtain a specimen of urine from this girl. The third patient had a normal family history, including two normal sisters.

The 17-ketosteroid levels varied from high normal to moderately elevated, and 17-ketogenic steroids were normal. However, in all three patients the urinary pregnanetriol was elevated, and in the two in whom it

was determined so was the 11-oxo-pregnanetriol. Since the determination of 17-ketogenic steroids includes both metabolites of cortisol and pregnanetriol with its 11-oxo-derivative, the urinary tetrahydrocortisone plus tetrahydrocortisol was determined and shown to be low in both instances. The effect of the injection of corticotrophin was evaluated in all three patients. The ratios 17-ketogenic steroids/17-ketosteroids were low in all cases (0.9–1.6) (Prunty *et al.*, 1958), but for unknown reasons the response to corticotrophin in Case 2 was definitely poor.

The results of therapy in these three patients were variable. Clinically the effect on the acne in Case 3 was dramatic and quite good in Case 1. In no case was the hirsutism abolished, but the alleviation varied from definite improvement in Case 1 to minimal improvement in Case 2. There was a definite tendency in all patients for the growth of hair to be softer, and this alone is often appreciated by patients. In general, the effects of treatment in prepubertal congenital adrenal hyperplasia are often gratifying and the acne and hirsutism which develop may be most favourably affected. Sometimes, however, probably especially if the inauguration of treatment is delayed, the reduction of hair growth is disappointing (Wilkins, 1957; de Mowbray *et al.*, 1959), as it often appears to be in post-pubertal hirsutism (de Mowbray *et al.*, 1959; Jefferies and Levy, 1959; Mattingly *et al.*, 1960) in spite of adequate suppression of 17-ketosteroid excretion by the treatment. This latter, of course, occurred in all three of the above patients (Table II, Fig. 2). In two of them 10 mg. of prednisone daily in divided doses was sufficient for the purpose, but in Case 3 it seemed necessary at times to raise the dosage to as much as 20 mg. daily. This dose is undoubtedly undesirably high and was sufficient to produce evidence of side-effects, whereas 10 mg. daily seems to be a perfectly safe dose.

Reference to Fig. 2 will show that there is a tendency for the administration of oestrogen alone to cause suppression of 17-ketosteroids in Case 1, and possibly also the pregnanetriol excretion. The addition of prednisone, of course, produces a more profound effect, but when the oestrogen is withdrawn on day 20 there is a temporary "rebound" of 17-ketosteroid excretion. Evidence of a similar effect of oestrogen has also been seen during the treatment of a patient aged 13 with congenital adrenal hyperplasia who normally excreted up to 100 mg. of 17-ketosteroid daily. On lowering the dose of cortisone to 37.5 mg. daily (Fig. 5) there was a steady rise in the excretion of 17-ketosteroid, which became markedly reduced on the simultaneous administration of 0.2 mg. of ethinyl oestradiol daily. There can be some similar effect of oestrogen in "simple hirsutism" (Mattingly *et al.*, 1960).

One of the most important aspects of these three cases is the nature of the lesion from which they are suffering. In spite of the late onset of clinical symptoms the biochemical pattern is typical of that of prepubertal congenital adrenal hyperplasia (Wilkins, 1957; Bush *et al.*, 1957; Finkelstein, 1959). Pregnanetriol excretion does not normally exceed about 1 mg./day and 11-oxo-pregnanetriol is below 50 μg. daily. Pregnanetriol may be elevated somewhat in some cases of simple hirsutism, and especially when corticotrophin is given, but the present cases may be distinguished from these by the relatively higher proportion of pregnanetriol to cortisol metabolites in the urine as reported by Brooks and Prunty (1960). These authors also report more detailed biochemical studies on these patients, indicating a pattern more typical of congenital adrenal hyperplasia than of simple hirsutism.

Description of patients of this type in the literature is scanty. It is not known what proportion of patients classified as having the adult adreno-genital syndrome by Broster and Vines (1953) have this abnormality of steroid metabolism. Finkelstein (1956) found 1 out of 11 virilized patients to be of this category, while Greenblatt (1958) has seen four similar patients, three of whom were sisters. This strongly substantiates the latter's view that these cases had a latent form of congenital adrenal hyperplasia. In one of our cases there is a strong probability of a familial background. From the biochemical point of view it is not certain that there is in fact a complete break between the pattern seen in the more severely abnormal cases of simple hirsutism and the least severely affected of the present cases (Brooks and Prunty, 1960), but there is no more direct evidence, other than the delay of clinical manifestation until puberty, that the lesion may be acquired.

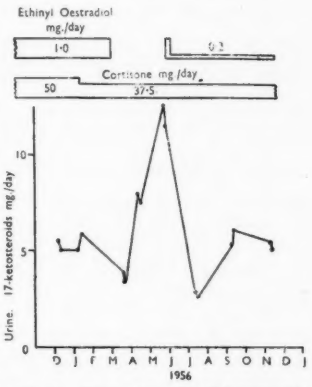

FIG. 5.—Excretion of 17-ketosteroid of a patient aged 13 with congenital adrenal hyperplasia. In the absence of treatment 17-ketosteroids reached 100 mg./day. Note the sharp drop in 17-ketosteroid when treatment with 0.2 mg. of ethinyl oestradiol daily was instituted in July, 1956.

It is not unusual for congenital biochemical lesions to occur in latent form, and there is some evidence that this may be true in parents of children with congenital adrenal hyperplasia (Childs *et al.*, 1956). Hence we are inclined to favour the view that patients with the adreno-genital syndrome of the type described here—that is, clinical post-natal adrenal virilism arising post-pubertally—have basically a congenital biochemical disorder of a type seen in congenital adrenal hyperplasia, where there is relatively greater or less deficiency of the synthesis of cortisol by the adrenal gland, and that this underlying defect could then possibly be brought to light by changing conditions at puberty. It is clear that, for the present at least, this group of patients can only be defined in biochemical terms and distinguished from patients with hirsutism of different origin (Prunty *et al.*, 1958).

Summary

Three cases are presented in which signs of hirsutism and virilism developed after the onset of puberty. This syndrome was accompanied by biochemical changes of the same nature as those found in congenital adrenal hyperplasia developing before puberty.

The urine contained an excess of pregnanetriol, which was accentuated by corticotrophin, excess of 11-oxo-pregnanetriol, and deficiency of metabolites of cortisol.

The nature of this condition and the importance of clearly clarifying it are discussed.

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TREATMENT OF SIMPLE HIRSUTISM, INCLUDING THE HIRSUTE TYPE OF STEIN–LEVENTHAL SYNDROME

BY

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The results of diminishing androgen production by steroid therapy or adrenal surgery, in patients with congenital adrenal hyperplasia and adrenal cortical tumour respectively, from the point of view of the hirsutism are variable. They may be dramatic, useful, or even disappointing (Hamilton and Shepardson, 1952; Blizzard and Wilkins, 1957; Heinbecker *et al.*, 1957; Prunty *et al.*, 1958).

In these patients there is usually a clear and major overproduction of adrenal ketosteroids. Occasionally in patients developing post-pubertal hirsutism there is an adrenal lesion similar to that seen in congenital adrenal hyperplasia (Brooks *et al.*, 1960). Such patients have been excluded from the present study. However, most patients suffering from post-pubertal hirsutism do not have these lesions. Many may be described as having simple hirsutism and some have the hirsute type of Stein–Leventhal syndrome with accompanying anovulatory menstrual cycles and sterility. In some of both of these groups abnormalities of adrenal ketosteroids may be demonstrated (Prunty *et al.*, 1958; Gallagher *et al.*, 1958; Brooks and Prunty, 1960).

The present paper concerns attempts at treatment of patients of these two latter types. The effect of prednisone, often combined with ethinyl oestradiol, on the hirsutism of these patients has been observed. While sometimes there is an undoubted favourable response, it must be stated at the outset that it is more often most disappointing. Hirsute patients with the Stein–Leventhal syndrome, the diagnosis being established as described previously (Prunty *et al.*, 1958), have more often been treated by ovarian wedge resection (Stein *et al.*, 1949), since this appears to be the treatment of choice for sterile married women.

Material and Methods

The patients studied included 21 of those described under the heading of simple hirsutism by Prunty *et al.* (1958) and three patients with the Stein–Leventhal syndrome having hirsutism. One of these three patients was included in the earlier paper under the heading of simple hirsutism. The presence of ovaries of the Stein–Leventhal type had been suspected, but at laparotomy they were found to be normal. Two years later she presented with a twisted ovarian cyst, at operation for which the ovaries were found to be typical of the Stein–Leventhal syndrome. Meanwhile she had irregular periods, but temperature records suggested she was ovulating during the few months immediately after the first laparotomy. All these patients were treated with steroids. Their approximate ages at onset of the hirsutism are given in Table I. The precise age at which it occurred is usually difficult to determine.

TABLE I.—*Age at Onset of Hirsutism*

Age in years ..	11–15	16–20	21–25	26–30	31–35
No. of patients	11	7	5	0	1

An additional seven patients with the Stein–Leventhal syndrome were subjected to ovarian wedge resection and not treated with steroids.

Twenty patients received 10 mg. of prednisone daily in divided doses; one received 30 mg., reduced to 20 mg.; one had 15 mg.; and one had 5 mg. In addition, 19 received ethinyl oestradiol in dosage between 0.05 and 0.3 mg. daily for three weeks in every four. Of these, 17 received either 0.1 or 0.2 mg. daily. The duration of steroid treatment varied from 4 to 39 months.

The urinary 17-ketosteroids were usually determined, often with two consecutive days' collection for each determination, to ensure that adequate suppression of 17-ketosteroids was maintained.

The assessment of changes in the hirsutism is not an easy matter. It is naturally most difficult, and undesirable, to prevent patients from removing their facial hair for a sufficient time to make an objective assessment of its rate of growth; the observer must therefore rely on patients' statements about frequency of removal. Bearing this difficulty in mind, patients in category 1 were said to have improved when there was a significant reduction in the frequency of the necessity for removal. This could sometimes be confirmed objectively. Patients who appeared to be certain that the hair, on their limbs particularly, was less virile were placed in category 2. All patients of category 1 also noted this feature. It was usual for all these patients to state that hair had become softer and lighter in colour. Patients in category 3 were those who received no benefit.

Results

Response of Hirsutism

Of the 24 patients on steroid treatment, six were classified in category 1, nine in category 2, and nine in category 3. There was one patient with the Stein–Leventhal syndrome in each category. In category 1 there was at least a doubling of the time intervals between shaving or electrolysis. The poorest response was from once daily to once in three days. The best response was a decrease of frequency of electrolysis from fortnightly to three-monthly intervals. This occurred after treatment for six months.

All patients in category 1 had had hirsuties for more than five years; four had urinary 17-kestosteroids initially exceeding 15 mg./day, two had levels less than these; three out of the four tested had abnormal responses to corticotrophin (Prunty *et al.*, 1958)—that is, the response ratio of ketogenic steroid/17-ketosteroid was less than 2/1.

In category 2 four were hirsute for less than five years, and five for longer; four had initial 17-ketosteroids above 15 mg./day and five less than this; seven responded abnormally to corticotrophin and one normally.

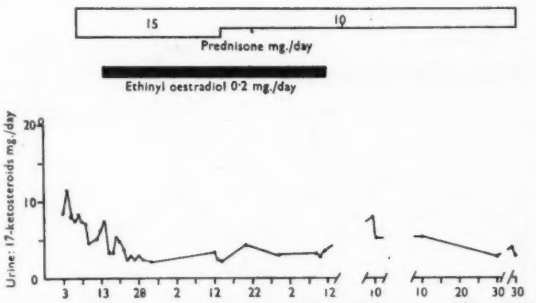
In category 3 four were hirsute for less than five years, five for longer; three had 17-ketosteroids above 15 mg./day and six less than this; two responded abnormally to corticotrophin and five normally.

The depression of 17-ketosteroid levels in these patients is shown in Table II: 11 out of 20 had levels below 3 mg./day.

TABLE II.—*Relation of Response of Hirsutism to Degree of 17-Ketosteroid Suppression*

	No. of Patients with 17-Ketosteroid mg. day		
	Less than 3	3–5	More than 5
Category 1 ..	3	2	1
,, 2 ..	5	1	1
,, 3 ..	3	3	1

It is not possible to draw definite conclusions concerning the effect of added oestrogen therapy. Of the five patients who did not receive oestrogen four were given 10 mg. of prednisone daily, and one had 30 mg. reduced to 20 mg. Three of the four for whom 17-ketosteroid data were available showed a depression to less than 3 mg./day, and two of these were in category 1 and one in category 2; the fourth patient was in category 3. The fifth in this group, receiving high steroid dosage, showed a depression of 17-ketosteroid to only 8 to 9 mg./day and was assigned to category 1.



Effect of prednisone, with and without additional ethinyl oestradiol, on suppression of urinary 17-ketosteroids in a patient with simple hirsutism.

The average doses of oestrogen were similar in all categories—0.12 mg./day for category 1, 0.11 mg. for category 2, and 0.14 mg. for category 3. The effect of oestrogen in one patient was studied carefully (see Fig.) It will be seen that there was a sudden decrease of 17-ketosteroid when oestrogen was added to treatment, and that a rebound occurred on withdrawal of the oestrogen.

Of the patients studied, three had a moderate degree of acne. All received oestrogen. There was significant improvement in this condition in two of these patients.

Patients with the Stein–Leventhal Syndrome

In our original series of hirsute patients there were nine with this syndrome. An additional patient can now be added for reasons described above. These 10 patients were subjected to ovarian wedge resection and in all of them menstrual periods returned to normal. From temperature records taken of seven all appeared to be ovulating. Six of the patients were trying to have babies and four succeeded in doing so within six months of operation. The operation did not appear to affect the hirsutism significantly.

Three patients have been mentioned above who received additional steroid therapy. Two of these began treatment after menstruation had returned to normal post-operatively, both receiving prednisone and oestrogen. In one the menstrual cycles remained regular, in the other they became slightly irregular. The third patient is the one mentioned above who was diagnosed later. Between operations she received prednisone only, and prior to wedge resection the periods remained quite irregular; subsequently they became regular and ovulatory.

Two of the patients with simple hirsutism became pregnant while on steroid therapy; one was receiving 0.2 mg. of ethinyl oestradiol, the other none.

Untoward Effects of Steroid Therapy

One patient developed mild hallucinatory symptoms which ceased when treatment was stopped. Three had some degree of menorrhagia while receiving ethinyl oestradiol, and this substance appeared to be associated with the development of migraine headaches in two others.

Discussion

There is no doubt that in the main the results of steroid therapy for hirsutism under the conditions of our observations were disappointing. This has been the experience of de Mowbray *et al.* (1959), who concluded that prednisone produced no striking improvement and that steroid therapy was not justifiable on the grounds of hirsutism alone. Others have been somewhat more enthusiastic (Perloff *et al.*, 1958), as have some observers using cortisone (see Jefferies and Levy, 1959). Our results have been variable and reminiscent of the disappointing responses seen in respect of the hirsutism in congenital adrenal hyperplasia. It is noteworthy, however, that it is often stated that the hair becomes softer and finer. This usually occurred with our patients, many of whom felt that it was a worth-while result, but in a few cases the improvement was certainly more striking than this. The less encouraging results of de Mowbray *et al.* (1959) may have been due to a

lesser 17-ketosteroid depression or a shorter time of treatment, together with a smaller number of patients.

The fact that some response was obtained, presumably by suppression of adrenal androgen production, supports the view that there is some abnormality in adrenal secretion in these patients (Brooks and Prunty, 1960). The 17-ketosteroids were well suppressed in nearly all patients, but even in spite of this many showed little or no improvement. There is a hint from the results that the response was best in those patients who responded abnormally to corticotrophin.

The effect of added oestrogen in the hirsutism could not be determined and we do not have the impression that under our conditions it was important. Nevertheless it is of theoretical interest that we have observed some synergism with prednisone on 17-ketosteroid depression, though this was relatively small. This effect has also been observed by Armstrong (1955) on combining stilboestrol and cortisone and by ourselves in the congenital type of adrenal hyperplasia (Brooks *et al.*, 1960).

The unfavourable results of ovarian wedge resection in the Stein–Leventhal syndrome on the accompanying hirsutism seems to be a frequent experience (Perloff *et al.*, 1958) though some observers have claimed to find favourable changes (Leventhal and Cohen, 1951). The fact that four out of six patients who were trying to become pregnant after wedge resection did so is in keeping with the 60% occurrence of this result observed by others (see Bailey, 1959).

Summary and Conclusion

The effects of prednisone therapy, usually 10 mg./day and usually combined with ethinyl oestradiol treatment, have been observed in 21 patients with simple hirsutism and three with the hirsute type of Stein–Leventhal syndrome. In six there appeared to be significant improvement, which was much more doubtful in a further nine.

In 10 Stein–Leventhal patients ovarian wedge resection was carried out by our colleagues. The results are discussed. Four out of six patients attempting to become pregnant did so within six months of operation.

In conclusion, while steroid therapy may benefit the occasional patient to a noticeable degree when a reasonably low dosage level is used, we do not feel that it is sufficiently beneficial to justify its use routinely. It is not yet possible to predict whether any particular individual will respond, and the problem of relapse on cessation of treatment also arises.

We are indebted to our several colleagues in the department of obstetrics and gynaecology who kindly performed the ovarian wedge resections.

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SOME EXPERIENCES WITH A NEW ANABOLIC STEROID (METHANDROSTENOLONE)

BY

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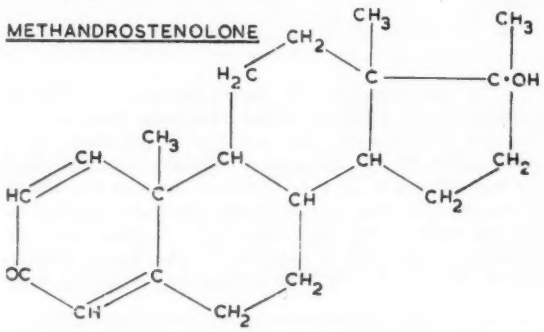
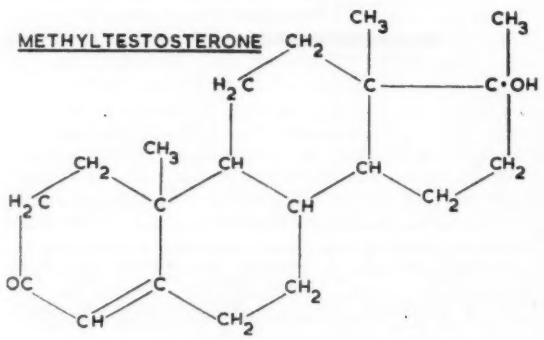
Considerable advances have been made in separating the androgenic from the anabolic effects of substances related to testosterone in recent years. Whereas in men there is no real advantage in having an anabolic hormone which is relatively non-virilizing, this is of great practical importance in therapy for women and for children of both sexes.

The development of these new steroids and their applications has been reviewed (Foss, 1959a, 1959b) with preliminary mention of 1-dehydro-17α-methyltestosterone.

Chemical Composition

Methandrostenolone (1 - dehydro - 17α - methyltesto - sterone; "dianabol") has the following structural formula, which is compared with that of methyltestosterone. Unlike methyltestosterone, there is double-bonding in the first benzene ring with loss of two atoms of hydrogen from carbons 1 and 2.





In rats its anabolic effect is as great as that of testosterone propionate or norethandrolone, but when tested for its androgenic effect it was approximately 100 times less active than testosterone propionate, and 17 times less active than norethandrolone in castrated rats. In the capon comb test it was 130–170 times less effective than testosterone propionate and 70–90 times less than norethandrolone.

Though these animal experiments with methandrostenolone have suggested that there is a considerable degree of dissociation of anabolic from androgenic effects, the potential hazard still exists in human subjects. In some of the clinical reports of early trials, in which rather large doses were used, mention is made of some virilization, particularly in children.

During the last year an attempt has been made to assess the magnitude of this effect in women, and in children when it was used for the stimulation of growth.

Material and Method

The subjects in this trial consisted of nine children or adolescent patients before growth had ceased (four females and five males) and four adult females. These were selected from hospital out-patients and private patients.

Careful records were made of changes in weight, height, and span; all measurements in each individual patient were carried out on the same instrument, and weights were recorded at the same time of day on the same machine. In some cases serial clinical photographs and skiagrams of epiphyses were taken before and during the course of treatment, and subjects were examined frequently.

At first only scored tablets of 25 mg. were available, but later tablets of 10 mg. were employed. The dose in mg./kg. was at first based on published reports of other anabolic steroids, and one's own experience with these or with methyltestosterone. As the trial proceeded some modification of this schedule was necessary.

Signs of androgenic effect were early lengthening and development of the penis and scrotum in prepuberal cases, early growth of fine hair around the base of the penis or on the pubes; deepening of the voice in adolescent males or in females; and any growth of fine hair on the upper lip or face.

In addition behavioural changes were noted in prepuberal males, such as embarrassment or shyness on being examined or a tendency to erection.

In women with regular menstruation a change in the cycle or delay or suppression of the menses was regarded as an androgenic effect.

Case 1

A female infant aged 1¼ years, the youngest child treated, birth weight 7 lb. 8 oz. (3.4 kg.), had always had a small appetite and was of flabby atonic build; weight 21 lb. (9.5 kg.), height 31½ in. (80 cm.). She was given methandrostenolone 25 mg. daily (2.5 mg./kg.). It was very soon apparent that this dose was excessive, as after 14 days she developed reddening, swelling, and discharge of mucus from the vulva. The dose was reduced to 12.5 mg. daily, with resolution of these effects. There was a remarkable change in her appetite. In six weeks of treatment she increased 2½ lb. (1.1 kg.) in weight and 1½ in. (3.8 cm.) in height.

Her progress has been followed for 43 weeks without further therapy, during which time she has had a net gain in weight of 5½ lb. (2.5 kg.) and an increase in height of 4½ in. (11.4 cm.) (Fig. 1). With this brief course of therapy there has been no further sign of precocity or virilization.

Case 2

A boy aged 4 years suffered from frequent attacks of bronchospasm, had a poor appetite, and was generally atonic. He was of normal proportions; weight 36 lb. (16.3 kg.), height 42⅛ in. (107 cm.). Methandrostenolone 12.5 mg. daily (0.73 mg./kg.) was given for 14 days; the dose was then reduced to 12.5 mg. on alternate days for nine weeks. During this period of 11 weeks he showed a net gain of 4 lb. (1.8 kg.) and his height increased by 1½ in. (3.8 cm.). His appetite was greatly increased and he was always hungry. After this treatment there was minimal lengthening of his penis.

After 40 weeks, however, his genital development was no different from that of any other child of his age, and during this time he had shown a net gain of 7 lb. (3.17 kg.) in weight and had grown 3½ in. (8.9 cm.) (Fig. 2).

Case 3

A boy aged 11 years had suffered with recurrent bronchitis. He had a poorly shaped chest with a marked Harrison sulcus, and his musculature was flabby. His appetite was poor. Weight 67 lb. (30.4 kg.), height 54 in. (137 cm.). He

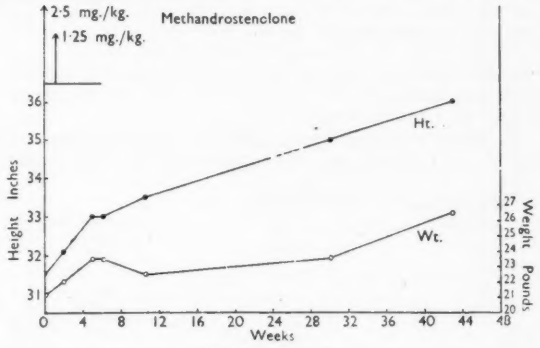


FIG. 1.—Case 1.

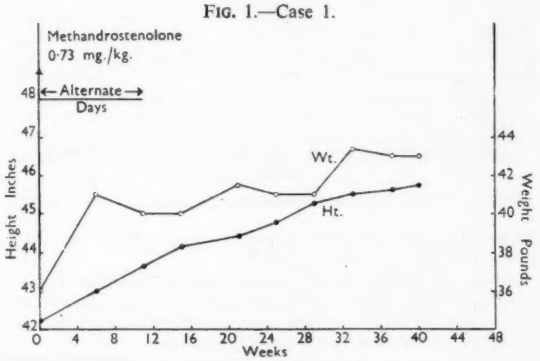


FIG. 2.—Case 2.

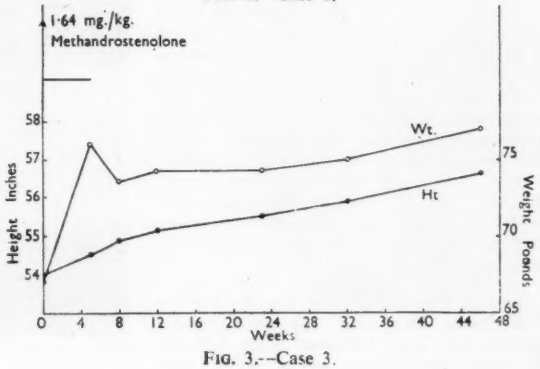


FIG. 3.—Case 3.

was given methandrostenolone 50 mg. daily (1.65 mg./kg.) for five weeks only. At the end of this period he was more robust and was always hungry. During this time he had gained 9 lb. (4.1 kg.) in weight and grown ½ in. (1.27 cm.).

There was minimal penile lengthening with fine hair around the base of the penis. Since withdrawing treatment there has been no further genital change or growth of pubic hair. Subsequent growth has been excellent, and in 46 weeks from starting therapy there was a net gain of 10 lb. (4.5 kg.) in weight and he had increased by 2⅜ in. (6.7 cm.) in height (Fig. 3).

Case 4

This child's growth and development had been followed since February, 1956, when at the age of 8 years 10 months he weighed 44½ lb. (20.2 kg.) and measured 44½ in. (113 cm.) in height—normal 58 lb. (26.3 kg.) and 51 in. (130 cm.). He was a healthy active child of rather short parents, and no organic cause was found to account for his small stature. After two years he was so concerned about his small size that it was decided to stimulate his growth with norethandrolone. A 10-weeks course of 10 mg. daily (0.45 mg./kg.) produced an acceleration of growth with a weight gain of 7 lb. (3.2 kg.) and an increase in height of 1 in. (2.54 cm.).

A second course of norethandrolone, increased after one month to 0.74 mg./kg. and maintained for nine weeks,

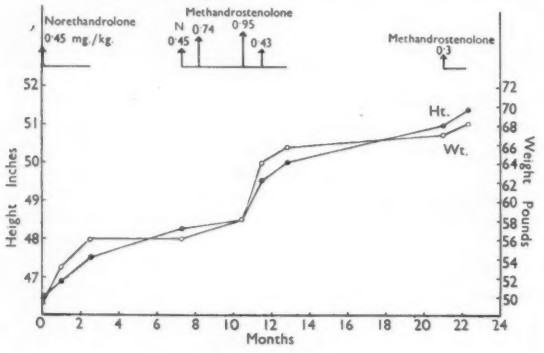


FIG. 4.—Case 4.

produced a much smaller response and he grew less than ½ in. (1.27 cm.) in three months.

At age 11½ years he was given methandrostenolone 25 mg. daily (0.95 mg./kg.) for a month and 12.5 mg. daily (0.43 mg./kg.) for a second month, during which time there was a gain of 7½ lb. (3.4 kg.) in weight and his height increased by 1½ in. (3.8 cm.) (Fig. 4).

At the end of the treatment with methandrostenolone, when he was 11 years 8 months, there was minimal lengthening of the penis with fine short basal peripenile down. He was also becoming self-conscious when weighed and measured, and attempted to cover his genitalia with his hands. After this the growth rate diminished, but, nevertheless, during the norethandrolone period he grew 2 in. (5.1 cm.) in 10½ months, and from the onset of methandrostenolone therapy he grew 2⅞ in. (7.3 cm.) in 11½ months.

Case 5

A foster child aged 11½ years, whose growth had been followed since he was 5¼ years, was about 4½ in. (11.5 cm.) below the normal average height, but the rate of growth was natural. He was active, fit, and healthy, but was inclined to be a problem child and was now very conscious of his small size in relation to boys in his class. He weighed 57 lb. (25.8 kg.), height 51½ in. (131 cm.), span 50 in. (127 cm.)—normal: weight 74½ lb. (33.8 kg.), height 56 in. (142 cm.), span 56½ in. (144 cm.). His proportions and genital development were normal for those of a boy of about 9½ years. *X*-ray examination of his epiphyses showed retardation equivalent to that of a boy of 9–10 years.

FIG. 5.—Case 5. Before (left) and after (right) 11 weeks' treatment with methandrostenolone 0.48 mg./kg.

Treatment with methandrostenolone 12.5 mg. daily (0.48 mg./kg.) was started, and after 11 weeks there was very minimal lengthening of the penis (Fig. 5) and he had gained 4 lb. (1.8 kg.) in weight and increased in height and span by ¾ in. (1.9 cm.). Treatment was stopped after 16 weeks. Penile lengthening was now definite, there was fine downy hair

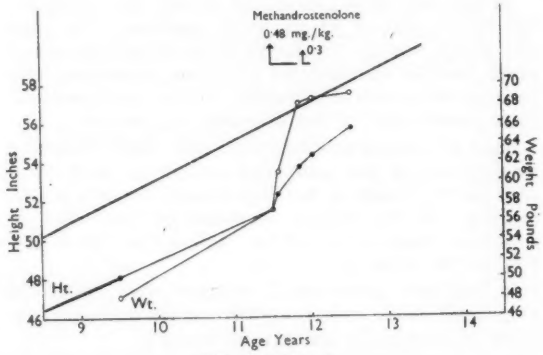


FIG. 6.—Case 5

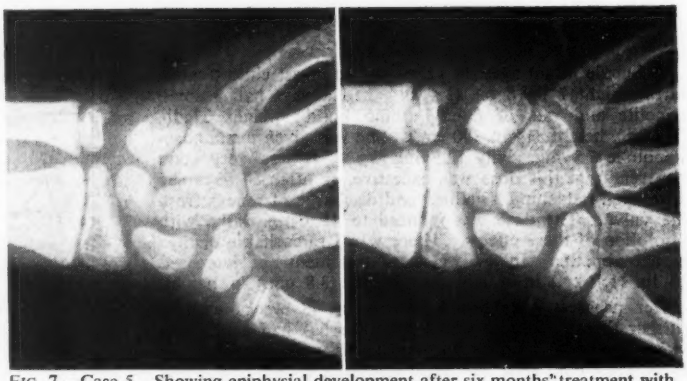


FIG. 7.—Case 5. Showing epiphysial development after six months' treatment with methandrostenolone.

over the pubes around the base of the penis, and early voice-change was apparent.

A second course was started, 10 mg. daily for one month (0.3 mg./kg.). His subsequent growth is shown in Fig. 6. Serial radiography showed quite an appreciable advance in maturation of the epiphyses and corresponded to those of a boy of 11 years (Fig. 7). The net gain in weight was 11½ lb. (5.2 kg.) and growth 2¾ in. (7 cm.) during six months' treatment.

Case 6

This girl's birthweight was 4 lb. 2 oz. (1.9 kg.), and owing to her diminutive stature and rather difficult childhood she had been under observation since birth. At the age of 9 years she had the appearance of progeria, but investigation showed no abnormalities; weight 37 lb. (16.8 kg.), height 45½ in. (116 cm.).

On June 4, 1957, it was decided to stimulate growth with thyroxine and methylandrostanolone. There was a satisfactory response, and in the next 17 months she grew 6 in. (15.2 cm.). Therapy was changed to norethandrolone 10 mg. daily (0.45 mg./kg.) and continued intermittently for six months, during which time she had grown another 1¼ in. (3.2 cm.).

When she was 11½ years methandrostenolone 10 mg. daily (0.37 mg./kg.) was substituted; weight 60 lb. (27.2 kg.), height 54½ in. (138 cm.). After 13 weeks she had increased by 1¼ in. (3.2 cm.) in height, and treatment was stopped. There was no facial hair; she had a normal voice, quite thick pubic hair, a trace of axillary hair, and there had been no change in epiphysial maturation in three months (Fig. 8).

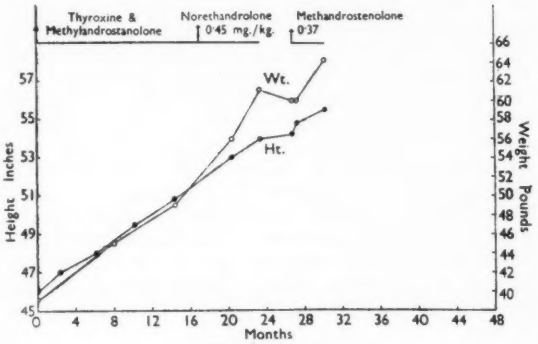


FIG. 8.—Case 6.

Case 7

This was a remarkable child with a rare type of dwarfism. 5 lb. (2.27 kg.) at birth, she had a history of recurrent chest infection since the age of 1 year. She was shown to have a ventricular septal defect with mild pulmonary hypertension, dwarfism, osteoporosis, and latent renal failure. Puberty occurred normally, and the menarche was at 12¾ years. *X*-ray examination of the skull showed calcification of her basal ganglia. Her case has already been published (Benson, 1959).

At 14 years she was a diminutive girl with small breasts and well-developed pubic and axillary hair and proportionate dwarfism: weight 50¾ lb. (23 kg.), height 46½ in. (118 cm.), span 51¼ in. (130 cm.)—normal: weight 101 lb. (45.8 kg.), height 61 in. (155 cm.). Menses were regular. *X*-ray pictures showed that epiphyses of the metacarpals and phalanges were beginning to unite, but the iliac-crest ossification was not present. All the bones were very small for her age.

An attempt was therefore made to stimulate growth, though she had been treated previously with methyltestosterone and had grown only ¼ in. (1.27 cm.) in the preceding two years.

Methandrostenolone was started on July 7, 1959, 10 mg. daily (0.43 mg./kg.) intermittently. After six weeks she had grown ⅝ in. (1.6 cm.). Her menses in July and August were suppressed during treatment, but started again on September 19, when treatment was withheld.

Case 8

At the age of 17¼ this girl weighed 82 lb. (37.2 kg.), height 53 in. (135 cm.), span 54¼ in. (138 cm.) and looked about 12–14 years, with no breast development and early labial hair. She was believed to be a case of ovarian dysgenesis with a high level of F.S.H., but both buccal cells and polymorphs were of the normal female type.

X-ray pictures of the epiphyses showed retarded development, with a bone age equivalent to that of a girl of 14. It was decided to try to stimulate growth for as long as possible with methandrostenolone and when the epiphyses had closed she would be treated with oestrogens and progesterone.

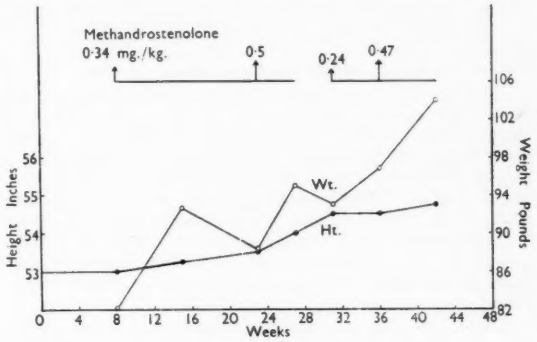


FIG. 9.—Case 8.

Methandrostenolone was started on April 7, 1959, 12.5 mg. daily (0.34 mg./kg.). After seven weeks she had gained 10 lb. (4.54 kg.) but grown only ¼ in. (0.64 cm.). The dose was increased to 0.5 mg./kg. for a month and continued intermittently with varying doses. 34 weeks after starting treatment she had gained 22 lb. (10 kg.) in weight and had grown 1¾ in. (4.45 cm.) (Fig. 9). There was minimal breast-budding, with a trace of hair at the corners of her upper lip. Pubic hair had increased and her voice was very slightly husky. Epiphysial development had scarcely altered in this time.

Case 9

An intelligent articled accountant was first seen at the age of 21½ years. He weighed only 105 lb. (47.6 kg.), but was of average height 66⅞ in. (170 cm.), span 66½ in. (169 cm.). His face and body were completely hairless and his

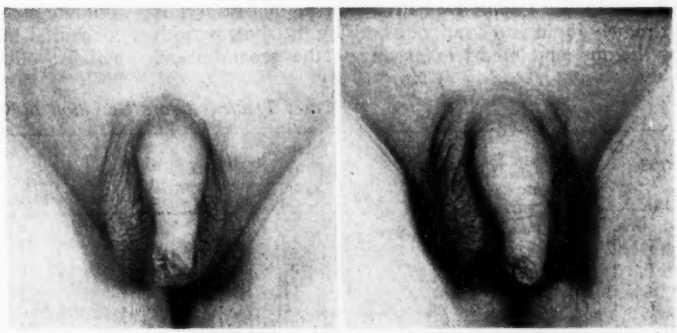


FIG. 10.—Case 9. Before (left) and after (right) 14 weeks' treatment with methandrostenolone 1 mg./kg.

skin was pale, smooth, and soft. He looked like a tall boy of about 12 years with no sign of genital development and with two infantile testes in the scrotum.

He had bilateral optic atrophy and bitemporal hemianopia, and an *x*-ray examination showed a large sella without erosion of the clinoids and no evidence of calcification in the pituitary region. Bone age corresponded to that of a boy of 12 years. 17-Ketosteroids were 2.9 mg./g. creatinine. Though there was slight evidence of impairment of thyrotrophic and corticotrophic factors the major feature was gonadotrophic deficiency, and while awaiting surgery it was decided to observe the effects of methandrostenolone.

After three weeks of 25 mg. twice daily (1 mg./kg.) erection occurred five or six times daily and minimal penile lengthening was noted. After a month the nipples were tender and slight subareolar thickening was apparent. After six weeks there was no increase in level of 17-ketosteroids (0.86 mg./g. creatinine). After 14 weeks on this dose he had gained 15 lb. (6.8 kg.) in weight and grown ¾ in. (1.9 cm.) in height. The serial photographs show the slight but definite androgenic effects (Fig. 10).

Methandrostenolone was continued throughout the period of operation and convalescence and then methyltestosterone was substituted in the same dosage.

Adult Female Cases

Case 10.—A woman aged 25, height 63 in. (160 cm.), had had both ovaries removed at 12 years for bilateral dysgerminoma and had subsequently developed a normal adult figure with oestrogens and cyclical progestogen therapy, weight 107 lb. (48.5 kg.) and wished to increase her weight. She was given a high-protein diet and methandrostenolone 0.5 mg./kg. for 12 weeks, during which time she gained 8 lb. (3.63 kg.). Her menses remained regular during this period, but she developed a greasy skin and several acne spots on her back. There was no hirsuties or change in her voice.

Case 11.—A woman aged 60 with osteoporosis of the spine, weighing 104 lb. (47.2 kg.), was given methandrostenolone 1.6 mg./kg. for 35 weeks except for an interval of six weeks. During this time there was only a net gain of 5 lb. (2.26 kg.). She has had no hirsuties or voice change at all up to the time of writing.

Case 12.—A woman aged 36 with regular menstruation was given methandrostenolone 25 mg. daily (0.5 mg./kg.) for 30 days. There was no suppression of menses and no sign of hirsuties or voice change.

Case 13.—A woman aged 43 who had had a radical mastectomy for breast carcinoma followed by deep *x*-ray therapy was given methandrostenolone 25 mg. twice daily (1 mg./kg.) for six weeks during which time she gained 4 lb. (1.8 kg.) in weight, but there has been no voice change or hirsuties, and her menses have continued without any alteration in the cycle or amount of loss.

Discussion

The effects of this anabolic steroid on the stimulation of growth are impressive; its action in this respect is extremely rapid and continuous during the short periods of therapy and seems to accelerate the general trend of growth when therapy is withdrawn. One of its main influences is the increase in appetite and a considerable gain in weight.

In the preliminary trials it soon became obvious that dosage was too high, and this was largely due to the fact that only tablets of too large a dose were then available. For children 5-mg. tablets are much more generally useful, as a dose of 0.1–0.3 mg./kg. should be sufficient. Short courses of treatment on these lines, repeated as necessary after an interval, will be satisfactory in most cases. Serial skiagrams are necessary to ensure that the bone age is not advanced by treatment, particularly when available linear growth is limited on first investigation of epiphysial maturation.

The use of methandrostenolone in premature infants may be of value in promoting protein anabolism at a phase when normally the infant should be growing at a greater rate than at any other time in life.

Metabolic balance studies have shown that methandrostenolone causes nitrogen retention with some retention of sodium and potassium during therapy (V. Wynn, 1958, personal communication).

Burke and Liddle (1960), in short-term metabolic studies in man, have assayed various synthetic analogues of testosterone for nitrogen-retaining activity, and methandrostenolone was shown to be about five times as potent as norethandrolone or methyltestosterone. Its stimulus to growth may be relative to the potency of its anabolic effect, and is similar to that which occurs with methyltestosterone therapeutically or with the normal androgens at puberty. However, largely bereft of its androgenic effect, it is possible that methandrostenolone may not cause premature closure of epiphyses, which is the normal result of puberty. Only long-term studies will show whether intermittent therapy with methandrostenolone in anabolic but relatively non-virilizing doses will produce growth ultimately greater than would be expected. Previously it has always been argued that therapy with methyltestosterone only produced an acceleration of growth similar to the puberty spurt, with an ultimate height the same as that which would have occurred without it, in the course of time.

It is likely that its effect in this respect is dependent on the complementary anabolic actions of thyroid hormone and insulin with adequate diet; but the absence of growth hormone may not matter, as with thyroid and methyltestosterone Hubble (1957) stimulated growth in primary hypopituitary dwarfs.

It is interesting to wonder whether the powerful anabolic stimulus of methandrostenolone would effect ultimate growth in dwarfism associated with mongolism, congenital heart disease, chronic renal disease, and the malabsorption syndrome.

Cases Treated Before Cessation of Growth

Case No.	Age	Sex	Weight		Height		Initial Dose	Growth with Methandros'enolone				Subsequent Growth from Onset		
			lb.	kg.	in.	cm.	mg./kg.	Weeks	% Wt.	in.	cm.	Weeks	in.	cm.
1	1¼	F	21	9·5	31½	80	2·50 (1·25)	6	12	1½	3·8	43	4½	11·4
2	4	M	36	16·3	42¼	107	0·73	11	11	1½	3·8	40	3½	8·9
3	11	M	67	30·4	54	137	1·65	5	13	½	1·27	46	2⅝	6·7
4	11½	M	58	26·3	48½	123	0·93	8	13	1½	3·8	48	2¾	7·3
5	11½	M	57	25·8	51½	131	0·48	26	20	2¾	7·0	48	4¼	10·8
6	11½	F	60	27·2	54½	138	0·37	13	7·5	1¼	3·2			
7	14	F	50¾	23·0	46½	118	0·43	6	0	⅝	1·6			
8	17½	F	82	37·2	53	135	0·34	34	28	1¾	4·45			
9	21½	M	105	47·6	66⅞	170	1·00	14	14	¾	1·9			

The accompanying Table shows that the unnecessarily high doses at first used in Cases 1, 2, and 4 produced 1½-in. (3.8-cm.) gain in height in 6, 11, and 8 weeks respectively, together with a percentage gain in weight of 12, 11, and 13. In these three cases and Case 3 there was definite slight androgenic effect during the course of treatment, which, however, did not progress when treatment was withdrawn. Subsequent growth continued at a very much higher rate than in untreated children of the same age.

In Cases 5, 6, and 8, in which doses of 0.34–0.48 mg./kg. were used, there was still a very useful stimulus to growth on longer or intermittent therapy with gains of 2¾ in. (7 cm.) in 26 weeks, 1¼ in. (3.2 cm.) in 13 weeks, and 1¾ in. (4.45 cm.) in 34 weeks, and a corresponding net percentage gain in weight of 20, 7.5, and 27. In Case 7 the growth had been only ½ in. (1.27 cm.) in the preceding two years, and the epiphyses were showing signs of incipient closure, and yet the patient gained ⅝ in. (1.6 cm.) in six weeks without a net gain in weight.

Evidence of commencing puberty was noted in Case 5, and in Case 7 two periods were suppressed during therapy, but normal rhythm was restored on withdrawal. In Case 8 there was slight increase in pubic hair and some dark fluff at the angles of the mouth with early areolar budding.

In Case 9, a young man of 21½, with the pituitary tumour and secondary hypogonadism, was an excellent test subject for evidence of androgenicity. On a continuous dose of 1 mg./kg. daily, objective signs of secondary sexual development were slight after three months. After a further three months the penis and scrotum were larger and scanty pubic hair was 1 in. (2.54 cm.) long and his voice was beginning to deepen. Treatment was then changed to methyltestosterone, and after seven weeks he experienced his first emission.

In adult females, Case 10 showed no suppression of menstrual rhythm while on her cyclical oestrogens and norethisterone. There was no sign of hirsuties or change of voice during 12 weeks' therapy with 0.5 mg./kg., but she did have some acne on her back.

An older woman, Case 11, was free from voice-change or hirsuties after continuous therapy with 1.6 mg./kg. for 35 weeks. Two other women given short periods of therapy for four to six weeks were not virilized in any way.

It would seem, therefore, that methandrostenolone in doses known to produce a good anabolic effect is almost free from androgenicity in women. On the other hand, there is no doubt that, in children, minimal signs of incipient virilization may be noted if the dose is above 0.5 mg./kg. and maintained for more than short periods. As a stimulus of growth. 0.2–0.5 mg./kg. is very satisfactory, and after about one to two months' therapy should preferably be withdrawn for three to four months.

Reports from the Continent (Pittman, 1959) claim that no virilization was seen in women with carcinoma of the breast or cervix treated with 200 mg. of methandrostenolone daily for four weeks. Most investigators used doses much larger than necessary at first, but it was reported that in children there was no significant virilizing action with daily doses of 1–2 mg./kg. (Pittman, 1959). There is little doubt, however, that these doses are much too big and that, if continued, will produce virilization. Though no signs of toxicity were seen even in adults given prolonged therapy, the possibility of cholostatic jaundice similar to that which sometimes follows treatment with norethandrolone or methyltestosterone (Foss and Simpson, 1959) should be remembered.

Summary

During the past year studies have been made on a group of nine children or hypogonadal patients and four adult females. Methandrostenolone has been shown to have a powerful anabolic effect, stimulating growth with increase in weight and height. There was evidence of continued acceleration of the growth pattern after withdrawal of therapy. For growth stimulation, doses of 0.25–0.5 mg./kg. were effective when given for short periods of four to six weeks; it may then be withdrawn for three to four months before giving a second course of treatment. However, on this regime signs of virilization were minimal, and in view of the results achieved they are of small concern. Smaller doses may well be adequate.

Even when at first unnecessarily large doses were used there were no prolonged androgenic effects.

Adult women showed no virilization with doses up to 1.6 mg./kg., and it is unlikely that higher doses are necessary.

I am indebted to Professor A. V. Neale for his interest and encouragement; to Dr. J. Apley and Mr. K. H. Pridie for allowing me to treat some of these patients; to Dr. A. K. Pittman for making available to me Ciba Research records and for supplying the dianabol, and to Mr. Godman, of the University Medical Photographic Department, for the clinical photographs.

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" One hundred and twenty years ago, in 1839, in a English city, expectation of life was very different from what it is to-day and very different for different classes. A baby born in a labourer's family might expect to live on an average 23.8 years; in the same city in a tradesman's home the baby might expect to live 30.8 years: if born in the home of the privileged gentry, its expectation of life was 48.6 years. By the turn of the century, the average figure for all classes had just passed that for the privileged of sixty years previously and stood at 48.5 for males and 52.4 for females. Judged by the criterion of expectation of life, to-day's most privileged babies are born in Holland, Sweden, and Norway, where the figures stand at 71, 70.5 and 69.3 respectively, closely followed by Australia, Denmark, New Zealand, Switzerland, United Kingdom, and United States of America. The underprivileged are born in India, where expectation of life at birth in 1950 still stood at 32.5 years, and India stands in this respect only at the bottom of a list of countries for which statistics are available. Where there are no statistics, it is likely that conditions are worse; for example, the indigenous population of Northern Rhodesia was estimated to have a crude death rate in 1950 of 32.2. Indonesia at the same time had an estimated rate of 20, and of this latter country it had been stated that an infant child dies every minute and a mother dies in childbirth every quarter of an hour. . . ." (Professor A. D. Munrow, University of Birmingham, at Unesco International Conference on the Contribution of Sports to the Improvement of Professional Abilities and to Cultural Development, Helsinki, August, 1959.)

ANTIDIURETIC PROPERTIES OF HYDROCHLOROTHIAZIDE IN DIABETES INSIPIDUS

BY

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Recently it has been stated that when experimental animals with diabetes insipidus are given hydrochlorothiazide the urinary volume is reduced by half (Kennedy and Crawford, 1959). This observation prompted us to assess the therapeutic response in a patient with diabetes insipidus who was loath to accept the prospect of daily injections of vasopressin. Treatment with hydrochlorothiazide reduced the urinary volume from 9.5 to 2.5 litres per 24 hours. The purpose of this paper is to record our investigations into the mechanism of this therapeutic paradox, and to assess the value of this drug in the management of patients with diabetes insipidus.

Case Report

A married woman of 33 was first seen in July, 1959. Two months previously symptoms of polyuria and polydipsia suddenly appeared and had persisted unabated. She had suffered no serious past illnesses, and her family were healthy. There were no physical signs of disease, and the urine contained no abnormal constituents. Her weight was 98 lb. (44.5 kg.), her height 56 in. (142 c.m.), and her blood-pressure 125/80. After 24 hours of fluid deprivation the urinary volume was 4 litres, with a specific gravity of 1006. Vasopressin tannate by injection effected a prompt reduction in the urinary output. A radiograph of the skull and an electroencephalogram were normal, and no cause for the diabetes insipidus was discovered.

Methods

At first the patient received an ordinary ward diet, but a measured intake of 10 g. of sodium chloride daily was substituted while the effect of salt replacement was studied. Fluid intake was unrestricted and no potassium supplements were given. The patient was weighed daily, and 24-hour urine collections were made throughout. Urine volume, specific gravity, and electrolyte excretion were measured daily; serum electrolytes were estimated twice weekly. On selected representative days plasma volume, glomerular filtration rate, and urine osmolarity were determined.

After a control period, during which no treatment was given, hydrochlorothiazide, 50 mg. twice daily, was administered until the maximum reduction in urinary output occurred. The drug was then discontinued and the patient allowed to return to control conditions. In order to elucidate whether hydrochlorothiazide acted by influencing salt excretion a further study was made; the same dose of hydrochlorothiazide was given, and the ensuing increase in urinary sodium loss in each 24 hours was replaced by oral sodium chloride. During the control period the mean daily sodium excretion was 135 mEq per 24 hours. This figure was subtracted from the urinary sodium content and the balance was replaced by sodium chloride in cachets. After discontinuing salt replacement the patient was discharged from hospital taking 50 mg. of hydrochlorothiazide twice daily on alternate days. Observation as an out-patient was continued, with a brief readmission to obtain a 24-hour urine collection.

Technical Methods.—Sodium and potassium were estimated by flame photometry; chlorides by potentiometric titration, using a silver electrode; and carbon dioxide by a manometric method. Glomerular filtration rate was determined by endogenous creatinine clearance, creatinine levels being estimated by the method of Løken (1954). Plasma volume was determined by dilution techniques with ^{131}I human serum albumin. Urine osmolarity was approximated from urea and electrolyte excretion.

Response to Hydrochlorothiazide

On the first day of treatment there was an increased loss of sodium and chloride, without any significant change in urinary volume (Fig. 1). On subsequent days sodium

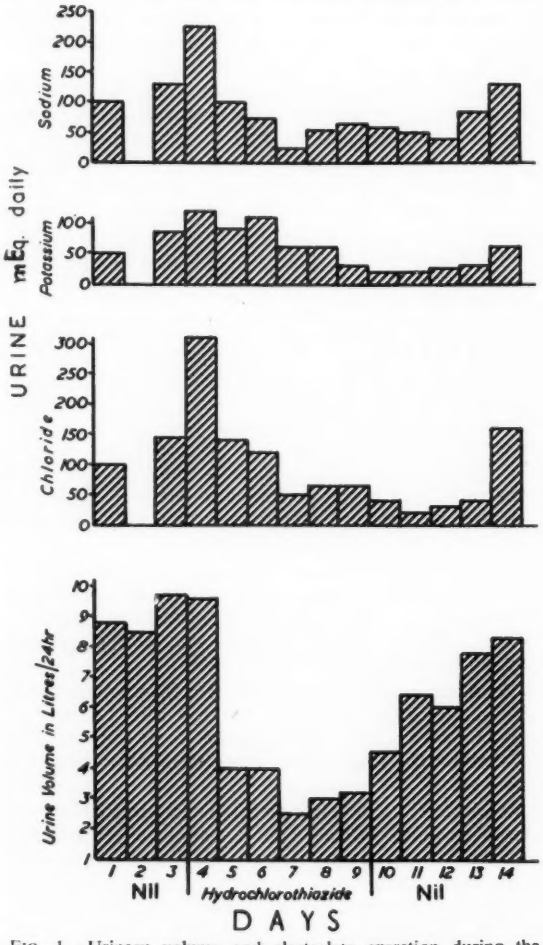

FIG. 1.—Urinary volume and electrolyte excretion during the administration of hydrochlorothiazide.

excretion fell to below the level observed before treatment commenced; this was associated with a reduction in urinary volume from 9.5 to 2.5 litres per 24 hours. Urinary potassium excretion was approximately doubled in the first few days of treatment, but thereafter the loss fell to control levels.

These changes were accompanied by a 20% reduction in plasma volume (from 2.2 to 1.76 litres) and by a 65% decrease in creatinine clearance (from 71 to 22 ml. per minute) (Table I). Over the same period the patient lost 5 lb. (2.3 kg.) in weight. Her diminutive size must be borne in mind, her surface area amounting to 1.3 square metres; to facilitate comparison the creatinine clearances are tabulated additionally corrected to a surface area of 1.73 square metres.

TABLE I.—*Plasma Volume, Glomerular Filtration Rate, Serum Electrolytes, and Urine Concentration After Administration of Hydrochlorothiazide*

Treatment	Urine Volume (ml./24 hrs.)	Weight lb.	Weight kg.	Plasma Volume (l.)	G.F.R. (Creatinine Clearance) (ml./min.)	G.F.R. Corrected to 1·73 sq.m. (ml./min.)	Serum Na+ (mEq/l.)	Serum K+ (mEq/l.)	Urine Osmolarity (m.osm./l.)	S.G. Corrected to 20° C.	Day
Hydrochlorothiazide ..	2,570	93	42·2	—	25	33	138	3·9	188	1007	7 (Fig. 1)
Nil	8,510	98	44·5	2·20	71	95	147	4·6	163	1005	2 (,, 2)
Hydrochlorothiazide ..	3,300	93	42·2	1·76	22	29	134	3·0	185	1007	8 (,, 2)

G.F.R. = Glomerular filtration rate.

The serum sodium level fell by 13 mEq/l. (Table I). There was a similar though smaller fall in the serum chlorides, and the alkali reserve increased by a few milliequivalents per litre. Serum potassium levels were reduced during treatment but never fell below 3 mEq/l. Urine osmolarity increased by 6.5% (from 163 to 185 m.osmols/l.), and the specific gravity of the urine rose from 1005 to 1007.

The blood-pressure did not alter significantly. An increase in the pulse frequency of 25 a minute constantly accompanied hydrochlorothiazide therapy, but this was not seen during the period of salt replacement. Though the urinary volume was not reduced to within normal limits, subjective improvement was considerable; thirst was reduced to the limits of comfort and the need to pass urine at night was relieved.

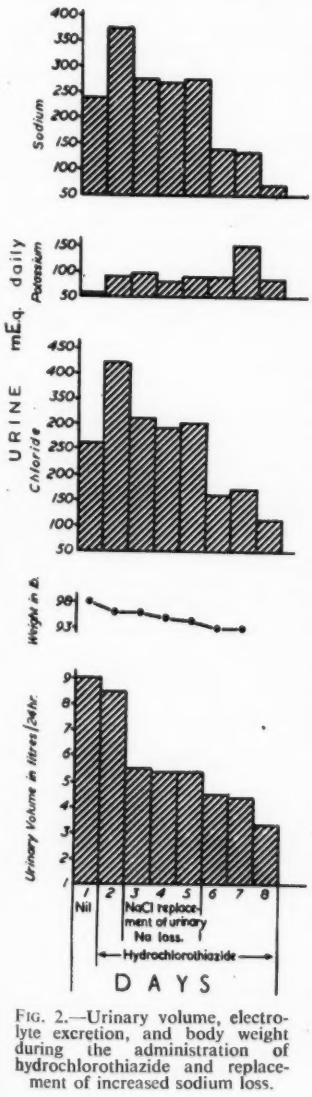

FIG. 2.—Urinary volume, electrolyte excretion, and body weight during the administration of hydrochlorothiazide and replacement of increased sodium loss.

Response to Salt Treatment

The antidiuretic effect of hydrochlorothiazide therapy was largely thwarted by replacing the increased urinary loss of sodium (Fig. 2). Approximately 5.5 l. of urine was passed each day. The creatinine clearance diminished from 71 to 45 ml. a minute, a reduction of 37% (Table II); and a loss of 2 lb. (0.9 kg.) in body weight was observed. Urine osmolarity increased from 163 to 223 m.osmols/l., a reflection of the added salt load being excreted, and in consequence the specific gravity increased to 1007. When salt replacement was discontinued the urinary volume diminished, being reduced to 3.2 litres per 24 hours three days after the extra salt was omitted.

Response to Hydrochlorothiazide Maintenance Therapy

Initially, subjective improvement was maintained while the patient received 100 mg. of hydrochlorothiazide on alternate days, but after three weeks symptoms of polyuria returned. When she was readmitted five weeks after leaving hospital the 24-hour urinary volume had risen to 6.9 litres and the creatinine clearance to 75 ml. a minute, and the specific gravity of the urine had fallen to 1004 (Table III). Serum electrolytes had returned to normal levels.

TABLE II.—*Glomerular Filtration Rate and Urine Concentration During the Administration of Hydrochlorothiazide and Replacement of Increased Sodium Loss*

Urine Volume ml./24 hrs.	Weight lb.	Weight kg.	G.F.R. (Creatinine Clearance) (ml./min.)	G.F.R. Corrected to 1·73 sq.m. (ml./min.)	Urine Osmolarity (m.osm./l.)	S.G. Corrected to 20° C.	Day
5.250	96	43·5	45	60	223	1007	4 (Fig. 2)

TABLE III.—*Glomerular Filtration Rate and Urine Concentration After Five Weeks' Treatment with Hydrochlorothiazide*

Urine Volume (ml./24 hrs.)	G.F.R. (Creatinine Clearance) (ml./min.)	G.F.R. Corrected to 1·73 sq.m. (ml./min.)	S.G. Corrected to 20° C.
6,900	75	100	1004

Discussion

The healthy kidney reabsorbs water by three distinct mechanisms operating in different anatomical sites. In the proximal tubule water diffuses passively through the tubular membrane along an established osmotic gradient. This "obligatory water reabsorption" comprises approximately 85% of the glomerular filtrate (Berliner *et al.*, 1958). In contrast to the proximal tubule, the distal tubule is relatively impermeable to water in the absence of antidiuretic hormone so that, though an osmotic gradient exists, little or no water may be reabsorbed. In the collecting tubules water is reabsorbed without solutes, so that this is the only site where a fluid hypertonic to the glomerular filtrate can be formed (Wesson and Anslow, 1952; Page and Reem, 1952). The most important contribution to the conservation of water is the change from dilute to isotonic urine under the influence of antidiuretic hormone on the distal tubule, for this may involve a change in water excretion of more than 10 ml. a minute. The further saving of water by the formation of a hypertonic urine in the collecting tubules is relatively small, amounting to only 1–2 ml. a minute (Berliner and Davidson, 1957).

A reduction in glomerular filtration rate, with ensuing diminution of the flow of urine to the collecting tubules, may alter the final urine concentration significantly. Indeed, it has long been realized that a concentrated urine may be formed in severely dehydrated dogs with diabetes insipidus (Shannon, 1942); and, more recently, del Greco and de Wardener (1956) and Berliner and Davidson (1957) have shown that in experimental animals with diabetes insipidus a reduction in glomerular filtration rate may be associated

with a fall in urinary volume and the formation of hypertonic urine. Furthermore, Kleeman *et al.* (1957), by lowering the blood-pressure of two patients with diabetes insipidus, reduced the urinary volume and increased its concentration to greater than that of the plasma. In all these experiments the glomerular filtration rate was reduced to 20–40% of normal. Smaller reductions in filtration might be expected to lower urinary volume without appreciably increasing the concentration, as occurs when patients with diabetes insipidus develop hypopituitarism (Leaf *et al.*, 1952); however, if hypopituitarism is complete the urine may even become hypertonic (Martin, 1959).

The beneficial effect of salt restriction on the polyuria of diabetes insipidus has long been recognized (Fitz, 1914; Beaser, 1947), though there is an unpredictable variation from patient to patient (Allen and Sherrill, 1923). This is in part the result of a reduction in solute load (Smith, 1951), but there is little doubt that depletion of blood volume follows salt restriction (McCance and Widdowson, 1937; Lyons *et al.*, 1946), and changes in extracellular volume result in marked changes in glomerular filtration rate (Cort, 1952).

Our studies of a patient with diabetes insipidus show that treatment with hydrochlorothiazide results in a marked reduction in urinary volume. This was preceded by a considerable loss of sodium and chloride in the urine on the first day of treatment. A 20% reduction in plasma volume and a loss of 5 lb. (2.3 kg.) in body weight were associated with these changes. The constant tachycardia which accompanied treatment with hydrochlorothiazide alone and its absence during the period of salt replacement suggest that it may be due to these changes. Provided hydrochlorothiazide does not directly affect creatinine metabolism the clearance of this substance may be used to demonstrate fluctuations in glomerular filtration. On this basis the glomerular filtration rate was reduced by 65% after treatment. The fact that the antidiuretic effect was delayed for 24 hours suggests that the reduction in glomerular filtration was predominantly the result of loss of salt and the ensuing diminution in plasma volume.

However, salt replacement of the increased urinary sodium loss did not entirely thwart the antidiuretic effect, and the glomerular filtration rate was reduced by 37% (Fig. 2 and Table II). This was probably due to the time interval elapsing before replacement began; hydrochlorothiazide exerted its action unimpaired for 24 hours before the urinary sodium content, and hence the amount necessary for replacement, was determined. On the other hand, the drug may have a primary action on the glomerular filtration rate, which is unrelated to electrolyte loss, as has been suggested by Januszewicz *et al.* (1959). We have found that chlorothiazide in a dose of 0.5 g. twice daily has a comparable effect, and this drug may have a similar primary action on glomerular filtration (Heinemann *et al.*, 1959). An injection of mersalyl (2 ml.) produced less marked reduction in urinary volume.

The patient's subsequent relapse during treatment with hydrochlorothiazide was accompanied by a rise in glomerular filtration rate and return to normal of serum electrolytes. This was probably not due to the reduced dosage, as the patient remained symptom-free for three weeks. It is possible that a compensatory mechanism of salt retention may have developed; in these circumstances an ensuing potassium loss might be anticipated.

It would appear, therefore, that the antidiuretic effect of hydrochlorothiazide in diabetes insipidus is predominantly the result of a loss of sodium and water with consequent reduction in plasma volume and glomerular filtration rate. A further reduction in glomerular filtration may be effected by a direct action of the drug not dependent upon electrolyte loss. We cannot suggest that hydrochlorothiazide has a major place in the management of patients with diabetes insipidus. This drug achieves a reduction in urinary volume with amelioration of symptoms, but vasopressin is obviously the treatment of choice, being the natural replacement of a hormonal insufficiency. Nevertheless, some patients tolerate vasopressin by injection badly, and in the form of snuff it may cause unpleasant rhinorrhoea or even asthma. Under these circumstances hydrochlorothiazide may be of value. The hazards of prolonged therapy with diuretics are well recognized, and in patients with diabetes insipidus receiving hydrochlorothiazide compensatory mechanisms of salt retention with ensuing potassium loss may be anticipated

Summary

The antidiuretic properties of hydrochlorothiazide in a patient with diabetes insipidus have been demonstrated. The effect has been shown to be chiefly the result of a urinary loss of sodium chloride and a consequent reduction in plasma volume and glomerular filtration rate. Hypokalaemia is a potential hazard of this form of therapy, and we believe that hydrochlorothiazide has little place in the management of patients with diabetes insipidus.

We thank Dr. K. O. Black for permission to study this patient; Dr. A. G. Spencer and Dr. J. C. B. Fenton for much helpful criticism and advice; Mrs. Eileen Akers for many of the chemical estimations; and Mr. N. K. Harrison for preparing the Charts. In addition, we thank the nursing staff for their willing co-operation.

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TREATMENT OF TUBERCULOUS MENINGITIS*

BY

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The incidence of tuberculous meningitis is at last rapidly diminishing in this country, yet in 1958 there were still 369 newly notified cases in England and Wales (Ministry of Health, 1959). As the untreated disease is inevitably fatal, this incidence is still an important therapeutic challenge. We can now look back on 12 years' experience in the treatment of tuberculous meningitis. In this time three main phases occurred as new specific antituberculous drugs became available. Furthermore, various adjuvants and neurosurgical techniques have been used with varying degrees of success.

Earlier Results

To place the current methods of treatment in perspective I shall briefly summarize the three main phases, on the basis of the personal experience of 210 children admitted to the Children's Hospital, Sheffield, between 1947 and 1958 (Table I). Most of these children were referred from other hospitals, and the composition of this series is weighted by advanced cases, which make up more than a quarter of the whole group.

TABLE I.—*Results of Treatment in* 210 *Children Admitted with Tuberculous Meningitis* (1947–58)

Antibiotic Treatment	Total No. of Cases	Alive			
		Total		No Neurological Sequelae	
		No.	%	No.	%
Streptomycin	82	30	36	20	24
Streptomycin+P.A.S. ..	48	35	73	30	63
Isoniazid, streptomycin, and P.A.S.	80	66	83	55	69
All forms	210	131	63	105	50

In the first phase, up to 1950, streptomycin was the only antibiotic available, and was used in prolonged intramuscular and intrathecal courses. Relapses were common. Sometimes hundreds of intrathecal injections were given (Illingworth and Lorber, 1951). We treated 82 children this way and 30 (36%) of them are alive now, but only 20 (24%) have no neurological sequelae.

The second phase was the combination of streptomycin with P.A.S., which was introduced in 1950 (Lorber, 1954a). This combination led to a considerable decrease in the number of intrathecal injections, but, even so, 10 out of 48 children each required the frightening total of 135 injections. The results were much better: 35 (73%) are alive now, and 30 of them (63%) have no neurological sequelae. This total figure hides the fact that all the improvement occurred in children who were conscious on admission (Fig. 1). Of 58 children who were treated with streptomycin alone and were conscious on admission 41% are alive, as compared with 86% of 37 treated with streptomycin and P.A.S. The proportion of survivors among those 35 who were unconscious on admission remained the same. Only one-quarter of these have survived and all have a residual neurological lesion.

Role of Isoniazid

The third phase started with the introduction of isoniazid in 1952 (Lorber, 1954b, 1956). Isoniazid is the most potent and least toxic of the antituberculous drugs. It freely diffuses into the C.S.F., so its intrathecal administration is only rarely necessary. As a consequence the need for prolonged courses of intrathecal streptomycin has been much reduced, though I know of no evidence to suggest that its use can be entirely abandoned with safety. Between 1952 and 1958 we treated 80 new cases with the combination of isoniazid, streptomycin, and P.A.S., and we progressively reduced the arbitrary minimum number of intrathecal streptomycin injections from courses of 45 to 25, then to 20, and now to only 10 injections. More intrathecal treatment is given if the clinical condition of the patient or the C.S.F. findings are unsatisfactory at any time after the conclusion of the 10 injections. Second intrathecal courses had to be given in their first attack to 15 children out of the 66 who survive, and tubercle bacilli reappeared in the C.S.F. in several of these while receiving by mouth 20 mg. of isoniazid per kg. body weight daily, even though they were in an early stage. These observations are my strongest argument against abandoning all intrathecal treatment. The overall survival rate in the 80 isoniazid-treated children is 83%. Of the 55 who were conscious on admission 52 (95%) survived and 50 (91%) have no mental or neurological sequelae. This represents a further advance on the

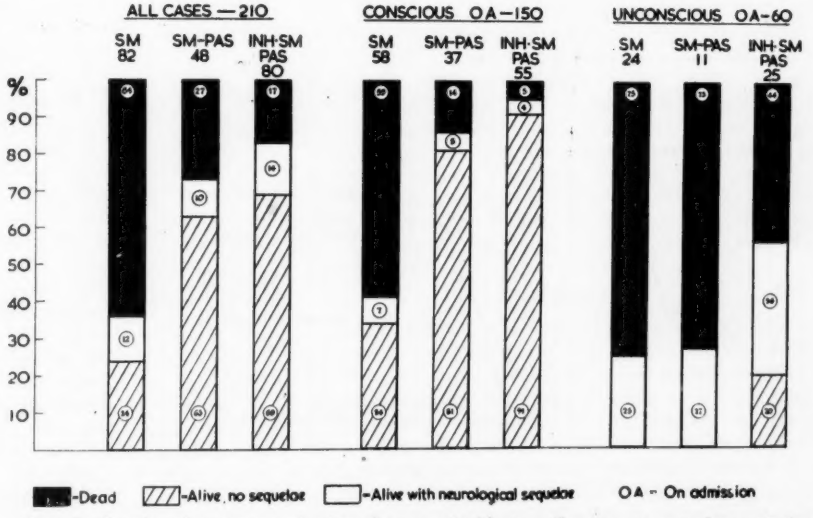

FIG. 1.—Results of treatment of tuberculous meningitis according to treatment given and the stage of consciousness on admission (1947–58). Minimum follow-up, 18 months.

*Read to the Section of Neurology and Neurosurgery at the Joint Annual Meeting of the British Medical Association and the Canadian Medical Association, Edinburgh, 1959.

good results achieved by the combination of streptomycin and P.A.S.

Of the three children who died, one was an 8-month-old infant who had combined tuberculous and influenzal meningitis; the second was an extremely emaciated boy of 7 years with advanced miliary tuberculosis and an established spinal block who went into uncontrollable status epilepticus shortly after admission. Both these received systemic and intrathecal cortisone as well, but it failed to save their lives. The third was a girl who died after a stormy course with gross disturbance of her electrolyte balance. Infarction of the adrenals was found at necropsy. This happened before the days of cortisone. It seems, therefore, that our current methods of treatment give satisfactory results in children who are conscious on admission, and uneventful recovery can be expected in almost all cases.

The situation, however, is still far from satisfactory in children who are in the advanced stage on admission (Table II). Out of 25 only 14 (56%) survive. At least,

TABLE II.—*Results of Treatment of Children Who Were Unconscious on Admission* (1947–58)

Antibiotic Treatment	No. of Cases	Alive			
		Total		No Neurological Sequelae	
		No.	%	No.	%
Streptomycin with or without P.A.S.	35	9	26	0	0
Isoniazid, streptomycin, and P.A.S.:					
Under 3 years old ..	16	8	50	0	0
3 years or older	9	6	67	5	55

this is a great improvement on the pre-isoniazid results, especially as five children have no neurological sequelae. All these five were over 3 years of age on admission. Of children who were unconscious and under 3 years of age on admission, we still have not been able to cure in 12 years a single child completely. It is clear that our main therapeutic efforts in the future must be directed towards finding better methods of treatment for this group.

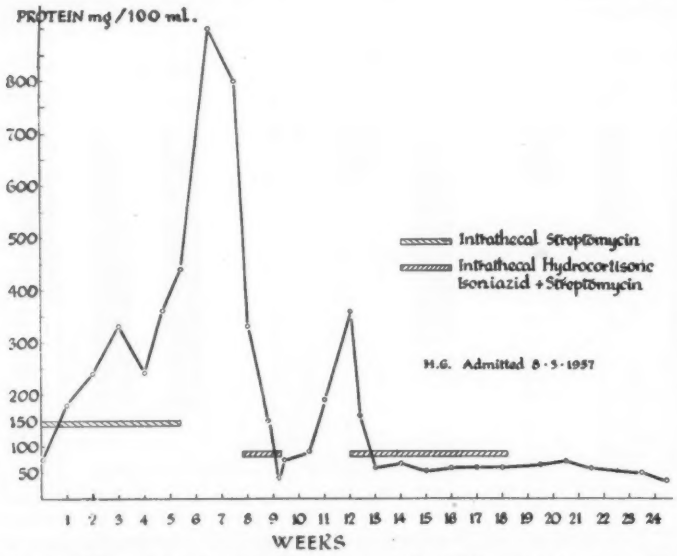

FIG. 2.—Effect of intrathecal hydrocortisone on the C.S.F. protein in a case with spinal block. The initial short course was followed by a relapse.

Seven children treated with isoniazid relapsed months or years after apparently complete recovery from their first attack. None of these were advanced cases on admission and all survived their second attack, though their clinical courses were often stormier, the duration of the disease and its treatment was longer, and in some the tubercle bacilli were much less sensitive to the main antibiotics than during their first attack. For this reason three of them were given intrathecal isoniazid to ensure a much higher C.S.F. concentration. Two children who made no headway on the three main antibiotics were given intramuscular viomycin with excellent effect when the sensitivity tests revealed that their tubercle bacilli had become very resistant to the three standard drugs.

Use of Adjuvants. Steroid Treatment

Among the important adjuvants, we used intrathecal tuberculin for several years in those patients who made poor progress on the standard treatment (Smith and Vollum, 1950). Occasionally it led to excellent results, but this form of treatment was a severe ordeal for the children, and was not without serious danger. When it appeared that cortisone or hydrocortisone might in some respects act in a similar way (Michel and Pulver, 1955) but without causing severe constitutional upset, we decided to use these drugs in selected cases in preference to P.P.D.

We now use systemic cortisone in all children who are either under 1 year of age or are unconscious on admission, as well as in all children who are severely toxic from advanced miliary tuberculosis. The duration of steroid treatment varies, but rarely exceeds one month. Intrathecal hydrocortisone is used in children with threatened or established spinal block. It is much more successful in restoring normal C.S.F. circulation in early than in well-established cases. The duration of intrathecal hydrocortisone treatment is determined by trial and error. If it is too short the C.S.F. signs of impending spinal block will reappear and can be reversed by a further course (Fig. 2). This is a very efficient treatment, but it is not free of danger. Secondary infection may be introduced, and, under cortisone cover, may remain silent both clinically and on examination of the C.S.F. For this reason we always combine intrathecal hydrocortisone with streptomycin, isoniazid, and penicillin in a "cocktail."

Altogether 15 patients have been treated with steroids up to 1958 and nine are alive (Table III). Of the six children who died I have already described two who were conscious on admission. A third baby survived, obtained a normal C.S.F., completed her treatment, and went home. She had severe mental and neurological sequelae, and died at home several months later of an unknown cause. The fourth and fifth had double meningitis, the second organism being the pneumococcus and staphylococcus respectively. These double infections were present at the time the children were admitted. Finally, the sixth child died a biochemical death. He developed a severe hypokalaemia which was not corrected even with intravenous administration of potassium. At necropsy the tuberculous meningitis

TABLE III.—15 *Children Treated with Corticosteroids as Adjuvant* (1955–8)

Route and Drug	Total	Alive and Well	Alive with Sequelae
Systemic cortisone	8	1	4
Systemic cortisone plus intrathecal hydrocortisone	5	2	1
Intrathecal hydrocortisone ..	2	1	0
	15	4	5

was found to be almost healed. This case illustrates one of the dangers of using drugs which may interfere with the electrolyte balance, and one must guard against this by frequent checks on the serum electrolytes, particularly in those treated with cortisone or viomycin.

It is not possible to show as yet in a statistically acceptable way that cortisone treatment contributed to the improvement of the results, particularly in our advanced cases. We cannot embark on a controlled trial as we no longer have sufficient cases to treat. We are satisfied, however, that used intrathecally it can prevent a threatened spinal block, and used systemically it can diminish the severe toxic state in the first few days of antibiotic treatment. None of our cortisone-treated children died in the first two weeks after admission, however deeply unconscious they were. In the past such children often died within a few days of admission and before antibiotic treatment had its full chance to exert its effect.

Current Treatment

To summarize our present routine of treatment (Table IV), it consists of a minimum six-months course of isoniazid by mouth, in divided doses of 20 mg./kg. daily together with 40 mg. of streptomycin per kg. given intramuscularly in a single daily dose. P.A.S. is given initially, but is continued for six months only if there are no side-effects. Viomycin is given twice weekly intramuscularly to children whose organisms are proved or strongly suspected to be resistant to at least one of the main antibiotics. Selected children are treated with cortisone according to the indications already outlined. The oral dose is up to 300 mg. daily, gradually reducing to 100 mg. daily, or its equivalent if any other corticosteroid is used. The dose of hydrocortisone intrathecally is 10–25 mg. according to age.

All children receive 10 intrathecal injections of streptomycin in doses of 20 to 50 mg. per injection. The first six are given daily, the others follow on alternate days. More injections are given if necessary. Intrathecal isoniazid is given to those who are given intrathecal hydrocortisone or whose organism is less sensitive to isoniazid. Pyridoxine (vitamin B_6) is given routinely in doses of 40 mg. daily to all children to guard against the neurotoxic effects of isoniazid. This is an essential precaution, as all the toxic manifestations of isoniazid, such as fits, disorientation, blindness, and paralysis, could easily be attributed to the complications of the meningitis itself. Finally, to guard against convulsions, which often have such disastrous effects, one must give full doses of anticonvulsants, at least until the child is well on the way to recovery.

TABLE IV.—*Current Treatment of Tuberculous Meningitis*

	Systemic	Intrathecal
Specific treatment:		
Isoniazid ..	20 mg./kg. daily for 6 months or longer	Occasional: 20–50 mg. per dose
Streptomycin ..	40 mg./kg. daily for 6 months or longer (maximum 1 g. daily)	10 injections (more if necessary): 20–50 mg. per dose
P.A.S.	If well tolerated: up to 5 g. daily	—
Adjuvant treatment:		
Cortisone (or other steroids)	1. In infants under 1 year of age 2. In all advanced cases for about 1 month	—
Hydrocortisone	—	In threatened or established spinal block
Pyridoxine ..	40 mg. daily	
Anticonvulsants	For 1–2 months	

The C.S.F. should be checked weekly at first, and later, when progress is obviously very satisfactory, at less frequent intervals, until one month after the discontinuation of treatment. No further examination is then necessary, unless there is the slightest suspicion on clinical grounds that all may not be well and a relapse is feared. If the child relapses, the second course of treatment should be longer, usually at least a year, and he will often require more intensive intrathecal treatment.

All this still sounds formidable, though it is trivial compared with the treatment which was given 10 years ago. Nevertheless, one would give a totally erroneous impression if one finished the description of our treatment with these technical details. In practice, things are much more cheerful. The large majority of children are much better within a week of admission, are afebrile, and are allowed to get up and play in a very pleasant ward which used to be the conservatory of a stately mansion. They wander into the adjoining playroom with its full array of toys and books for all ages and its television set. Alternatively, in good weather they will go through the french windows into an extensive garden where they play games. Teachers look after children of school age and they start their lessons within a week or two of admission. We have even had children taking their 11-plus examination while still under treatment.

We do not like to keep small children in hospital and away from their families a day longer than is essential. Pre-schoolchildren who live in the city or not too far out are therefore sent home after the first month of treatment if they are well, and they receive their daily injections from a health visitor. Their treatment is supervised from the out-patient clinic and the C.S.F. is checked at their attendances. This policy is very popular, and we had good co-operation from the family doctors, health visitors, and the parents, and so far have had no cause to regret this liberal approach. We prefer to keep children of school age in hospital longer, because otherwise their education would be unnecessarily interrupted. When we do send them home they are ready to resume ordinary attendances at school the next day.

Summary

In the course of 12 years 210 consecutive children were admitted and treated for tuberculous meningitis. Of these 131 (63%) survived, and 105 (50%) have no neurological or mental sequelae. The results progressively improved with increased experience in management, and with the introduction of P.A.S. followed by isoniazid as specific anti-tuberculous drugs and P.P.D. and corticosteroids as adjuvants. Since the introduction of isoniazid 66 out of 80 children (83%)

survived, and 55 of them have no sequelae. The most difficult patients are those who are under 3 years of age and are unconscious on admission, and none of those so far have made a complete recovery. Intrathecal streptomycin treatment has not been abandoned, but the minimum course is now reduced to 10 injections. The total duration of treatment is six months or longer, but most of this time the children are ambulant and either are treated at home or receive regular schooling in hospital. Systemic corticosteroids are used in children under 1 year of age or in those who are unconscious on admission; intrathecal hydrocortisone is of value in threatened or established spinal block.

The work on which the paper is based has been continuously in progress over 12 years. It would never have been possible without the continuous help and confidence of Professor R. S. Illingworth and without the selfless contribution of many colleagues in the region who referred their patients to us for treatment.

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UNILATERAL EMPHYSEMA

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An apparent increase in the transradiancy of one lung may be due to rotation, to diminished contralateral transradiancy, to giant cysts or bullae, to compensatory emphysema, or to obstructive emphysema resulting from incomplete bronchial occlusion. Macleod (1954) described a group of cases showing abnormal transradiancy of one lung in which none of these causes was apparent. The purpose of this paper is to report the radiological and physiological characteristics of seven patients conforming to Macleod's original description. These patients had all been referred with respiratory symptoms to the out-patient clinics of the London Hospital over a period of two years.

Methods

The study of each patient included clinical history and examination, postero-anterior radiographs in inspiration and expiration, fluoroscopy, whole-lung tomography, and either bronchography or bronchoscopy. The following physiological measurements were made:

1. The subdivisions of the lung volume, residual volume being measured by a closed-circuit helium-dilution technique (Bates and Christie, 1950).

2. The maximum breathing capacity expressed as the maximum voluntary ventilation at a respiratory rate of 80 per minute (M.V.V.80). This was repeated after an inhalation of 1% isoprenaline sulphate to assess the degree of reversible bronchial obstruction.

3. The maximum inspiratory and expiratory flow rates, derived from the spirometric tracing of a forced inspiration and expiration respectively.

4. Mixing efficiency, calculated from the helium-dilution curve (Bates and Christie, 1950).

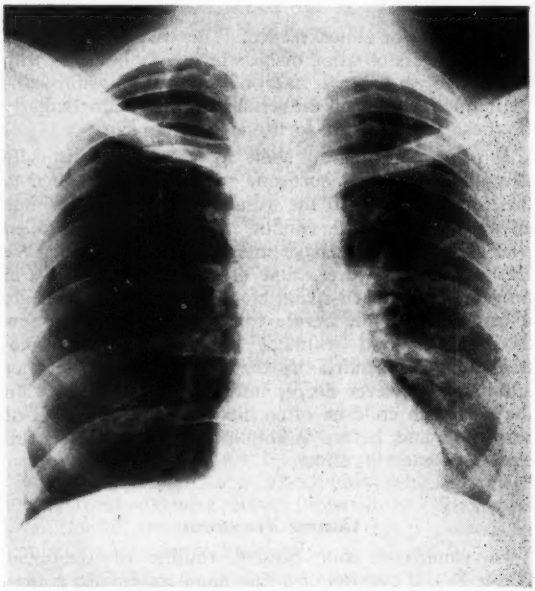

FIG. 1.—Case 4. Postero-anterior radiograph showing increased transradiancy of right lung.

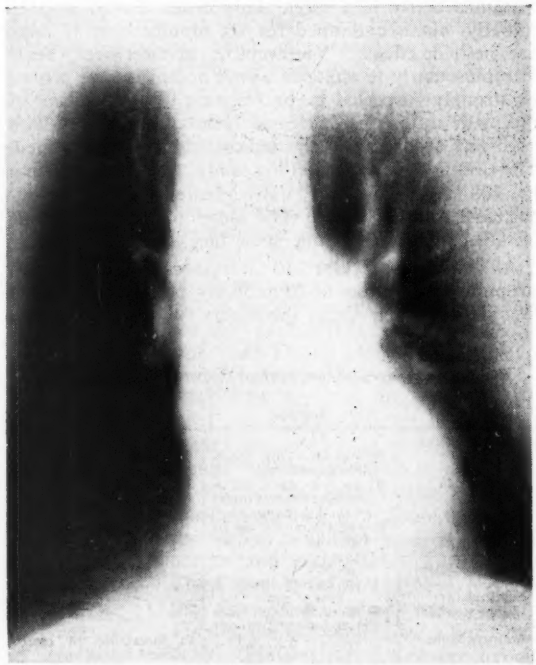

FIG. 2.—Case 2. Whole-lung tomogram showing diminished vascularity of right lung most marked in middle and lower zones. Note also low flat diaphragm on this side.

5. The diffusing capacity, measured by the single-breath carbon-monoxide technique (Ogilvie, Forster, Blakemore, and Morton, 1957).

6. The differential function of the two lungs was measured by bronchospirometry in one patient.

Results

The radiological findings are recorded in Table I and Figs. 1 and 2, and the physiological findings in Tables II and III and Figs. 3 and 4.

There were five men and two women, with an average age of 52 (range 38–70 years). All gave a long history of recurrent cough and exertional dyspnoea, and six had suffered attacks of pneumonia or pleurisy in earlier life, four of them in childhood. Except for one patient (Case 6) with severe disability, dyspnoea was of mild to moderate degree (grade 1 or 2). Diminished breath sounds over a part or the whole of the affected lung were noted in each patient.

TABLE I.—*Clinical and Radiological Findings in Seven Patients with Unilateral Emphysema*

Case No.	Age	Sex	Past Health	Transradiant Lung	Diaphragm on Abnormal Side	Resting Mediastinal* Position	Main Site of Narrowed Vessels	Bronchography
1	70	M	Pneumonia twice	Right	Low, diminished movement	Right	R.M.Z. R.L.Z.	—
2	51	M	,, three times in childhood	,,	Low, flat, diminished movement	Central	,, ,,	R. lower lobe bronchial crowding. No obstruction or bronchiectasis
3	46	F	"Born with bronchitis." Pleurisy at 6 years	,,	,, ,, ,,	Left	,, ,,	Normal apart from poor peripheral filling
4	46	F	Pneumonia at 9 months. R. pneumonia at 35 years	,,	Diminished movement	Right	Throughout R. lung	R. lower lobe bronchial crowding. No obstruction or bronchiectasis
5	38	M	Pneumonia in childhood. Off school with chest trouble from 5 to 7 years	,,	Low, flat, diminished movement	Central	R.M.Z. R.L.Z.	—
6	55	M	Pneumonia at 25 years	Left	Diminished movement	,,	L.U.Z. L.M.Z.	—
7	60	M	—	Right	,, ,,	Right	R.M.Z. R.L.Z.	—

* Mediastinal deviation toward the affected side on inspiration and away on expiration was noted in every case.

TABLE II.—*Pulmonary Function Tests in Seven Patients with Unilateral Emphysema*

Case No.	Vital Capacity (ml.)	Funct. Residual Capacity (ml.)	Residual Volume (ml.)	Total Lung Capacity (ml.)	R.V.: T.L.C. Ratio	Maximum* Breathing Capacity (l./min.) (M.V.V.80)	Swept Fraction	Maximum Inspiratory Flow Rate (l./min.)	Maximum Expiratory Flow Rate (l./min.)	Mixing Efficiency	Diffusing Capacity (% of Normal)
1	2,900	3,075	2,475	5,375	46%	45 (52)	18%	102	95	15%	41%
2	2,620	3,550	2,950	5,570	52%	75 (91)	34%	300	56	15%	80%
3	1,850	3,220	2,570	4,220	61%	49 (54)	27%	150	107	15%	110%
4	1,805	2,600	1,870	3,675	51%	52 (64)	31%	105	48	46%	83%
5	3,285	3,865	3,030	6,315	48%	62 (73)	21%	150	88	18%	83%
6	2,445	6,268	5,403	7,848	69%	26 (33)	13%	167	17	18%	55%
7	3,680	—	—	—	—	72 (81)	30%	221	92	—	77%
Mean ..	2,655	3,763	3,050	5,501	55%	54 (64)	25%	171	70	21%	76%

* Figures in parentheses indicate M.B.C. after isoprenaline.

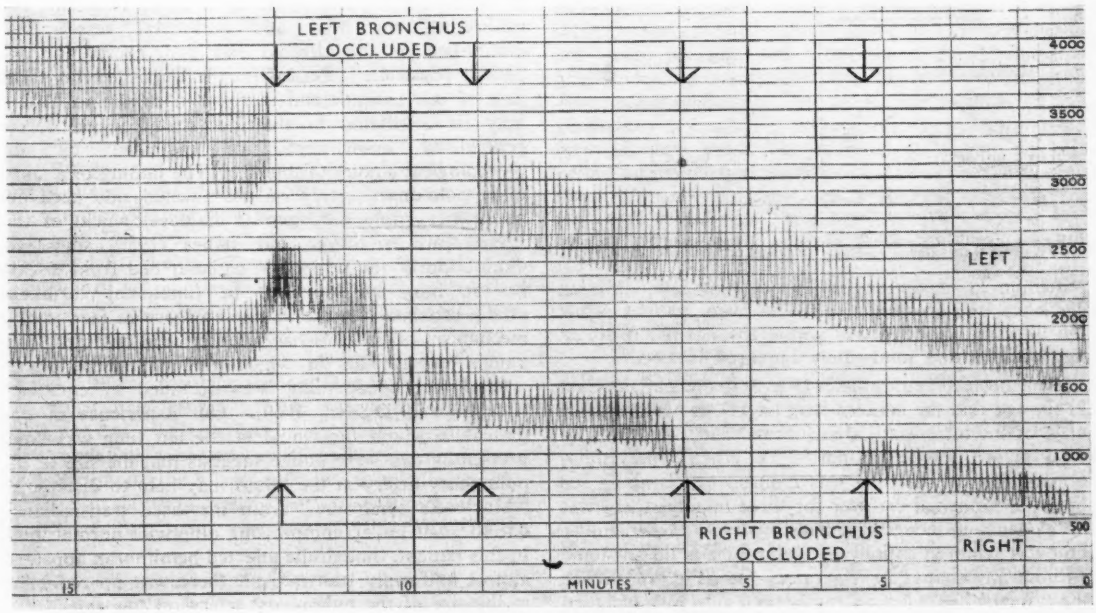

FIG. 3.—Bronchospirometric studies in Case 2.

Chest radiographs (Figs. 1 and 2 and Table I) showed increased transradiancy of the right lung in six patients and of the left lung in one (Case 6). Calcified hilar glands were observed on the affected side in three patients, and in one (Case 6) a strand of fibrosis extended from the hilum into the upper lobe. In each patient there was diminished excursion of the diaphragm dome on the affected side, with depression and flattening in four cases. The position of the mediastinum at rest was variable, but in every case the mediastinum deviated toward the affected side on inspiration and away from it on expiration. Whole-lung tomography demonstrated a decrease in the calibre of the main pulmonary artery and of the peripheral vessels on the affected side, with (except in Case 6) an apparent increase in calibre on the opposite side. The greatest reduction in vessel size was observed in the middle and lower zones of the right lung in five patients, throughout the right lung in one patient, and in the upper and middle zones of the left lung in one (Case 6). Bronchography revealed crowding of the right lower lobe bronchi, without apparent obstruction or bronchiectasis, in two patients, and in a third the pattern was normal, except for poor peripheral filling.

Physiological studies (Table II) revealed an increase of residual volume at the expense of vital capacity, so that in each patient the ratio of residual volume to total lung capacity was much increased. The maximum breathing capacity (M.V.V.80) was reduced in every case, and the slight increase after a bronchodilator drug (5–16 l./min.) suggested that there was only a small element of reversible bronchial obstruction.

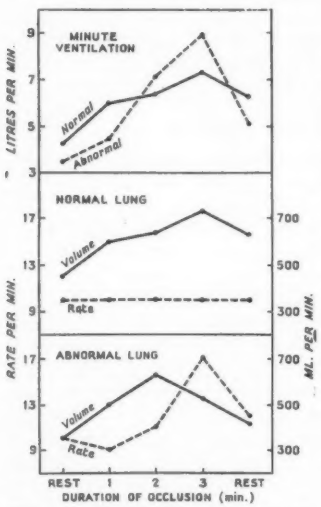

FIG. 4.—Ventilatory effects of unilateral bronchial occlusion.

The low "swept fraction" (D'Silva and Kazantzis, 1954) indicated that the maximum breathing capacity was impaired relatively more than the vital capacity. The reduction in maximum expiratory flow rate was in every patient greater than the reduction in maximum inspiratory flow rate. Mixing efficiency was grossly impaired in every patient, while the diffusing capacity was within the normal range in five patients and moderately impaired in two.

Bronchospirometric studies (Fig. 3) in one patient (Case 2) showed that the affected lung (right) was contributing 43% of the total ventilation (normal 55%) and 39% of total oxygen uptake (normal 55%). When hyperventilation of the normal lung was induced by clamping the opposite bronchial catheter for three minutes there was little change in the resting expiratory level. Hyperventilation was achieved entirely by an increase in tidal volume without any change in respiratory rate (Fig. 4). When the bronchial catheter on the normal side was occluded for three minutes, hyperventilation of the abnormal lung was accompanied by progressive overinflation of the lung, as indicated by the sharp rise in the resting expiratory level. The rapid fall in the resting expiratory level at the end of the three-minute period shows that this change was not due to increasing oxygen uptake. Hyperventilation of the abnormal lung was achieved at first by an increase in tidal volume and later by a marked increase in rate associated with a decrease in tidal volume, presumably due to progressive distension of the lung limiting further increases in volume. It is of interest that for at least three minutes after this manœuvre there was no oxygen uptake from the abnormal lung even though normal ventilation had been resumed.

Discussion

The clinical and radiological patterns observed in these seven patients are similar to the description given by Macleod (1954) and by Dornhorst, Heaf, and Semple (1957). In all three series the majority of patients complained of exertional dyspnoea; diminished breath sounds and hyperresonant percussion note were found over the affected lung. Men were affected about three times more often than women. The three series also have in common the findings of increased transradiancy of one lung, diminished hilar and peripheral vascular shadows, and poor expiratory deflation in the absence of either gross bronchial obstruction or diffuse bullous changes. In several cases poor peripheral filling or localized bronchial crowding was observed in the bronchogram. A remarkably high incidence of pneumonia in early life was noted in the series of Dornhorst *et al.* as in ours, but Macleod does not mention the previous health of his patients. Dornhorst *et al.* recorded six attacks of pneumonia in early childhood in three of their four patients, while we recorded 11 attacks in six of our seven patients, seven occurring in early childhood.

The vascular pattern in our seven patients, as revealed by whole-lung tomography, is of some interest. The calibre of the hilar and peripheral vessels was diminished on the affected side and, except for one patient (Case 6), increased on the opposite side. The lack of this contralateral increase in calibre in Case 6 may be attributed to the fact that he had severe generalized emphysema, as indicated by the physiological studies (Table II). The finding of a small main pulmonary artery on the affected side need not necessarily imply a congenital maldevelopment of this vessel, for, as Swyer and James (1953) suggested, diminution of the peripheral vascular bed from disease in the lung might result in functional shrinkage of the proximal vessels. Some evidence in favour of a mechanism of this sort has recently been obtained from animal experiments in which part of the peripheral arterial tree of one lung was occluded by embolism (Fouché and D'Silva, 1960). Our experience of one patient in whom the whole of the left lung was compressed by two large bullae suggests that the size of the pulmonary artery at the hilum may help to distinguish "Macleod's syndrome" from increased transradiancy due to giant bullae compressing otherwise normal lung. In this patient, though the affected hemithorax appeared almost uniformly transradiant, there was no reduction in the size of the pulmonary artery on this side.

TABLE III.—*Pulmonary Function Tests: Normal Values, Unilateral Emphysema, and Generalized Emphysema*

	Vital Capacity (ml.)	Funct. Resid. Capacity (ml.)	Resid. Vol. (ml.)	R.V.: T.L.C. Ratio	Maximum Breathing Capacity (in l./min.) (M.V.V. 80)	Swept Fraction	Maximum Inspiratory Flow Rate (l./min.)	Maximum Expiratory Flow Rate (l./min.)	Mixing Efficiency	Diffusing Capacity
Normal	3,500	2,700	1,500	30%	120	35%	300	400	70–90%	70–120%
"Unilateral transradiancy" (7 patients)	2,655	3,763	3,050	55%	54	25%	171	70	21%	76% (normal in 5)
Emphysema (20 patients)	2,380	4,960	4,025	62%	30	20%	144	30	28%	60%

Tomography has also demonstrated that the reduction of vessel calibre is not uniformly distributed throughout the lung. In five of our seven patients the vessels of the middle and lower zones of the right lung were predominantly affected. It may be relevant that this is the site most often affected by bronchial obstruction in childhood, whether due to foreign body or to tuberculous hilar lymph nodes. Six of our seven patients had one or more attacks of "pneumonia" in earlier life, and the radiographs of three of them demonstrated calcified lymph nodes at the hilum on the affected side. These observations suggest that temporary bronchial obstruction in childhood may have damaged the parenchyma of the affected portion of lung, which in later life could result in overexpansion and impaired deflation because of loss of elastic recoil in expiration. An alternative explanation in those cases showing bronchial crowding is that there is "compensatory" emphysema of the parts not subjected to obstruction.

The physiological pattern in these seven patients differs only in degree from that observed in 20 patients (of the same age group and sex distribution) with classical chronic diffuse obstructive emphysema. The values obtained in "unilateral hypertransradiancy" are, with the exception of mixing efficiency, intermediate between the normal values and those found in generalized emphysema (Table III). The greater impairment of mixing efficiency in the unilateral disease could be attributed to a gross disparity in the rate of ventilation of the two lungs.

The diffusing capacity was impaired in one patient with severe disability and physiological evidence of generalized emphysema, and in another patient, who was the oldest in the series (70 years). It was within the normal range in five of the seven patients. This finding suggests that there must still be a considerable diffusion contribution from the affected lung or that the remainder of the capillary bed has successfully accommodated the increased blood-flow diverted to it. It is thus in keeping with the radiological observation of continued perfusion of parts of the affected lung and the increased vascularity of the normal lung. The fact that the lungs of these patients are able to maintain a normal diffusing capacity also suggests that the original fault must have arisen at an early age, when the remainder of the capillary bed was capable of accommodating a considerable increase in blood-flow. After pneumonectomy for carcinoma in middle age, the reduction in diffusing capacity is commensurate with the amount of lung tissue removed (McIlroy and Bates, 1956).

Bronchospirometric studies in one patient (Case 2) showed that there was a significant, though reduced, contribution to function on the affected side. The period of suspended oxygen uptake which followed overdistension of the abnormal lung during hyperventilation suggests that blood-flow was temporarily diverted to the opposite side. This observation, taken in conjunction with the finding of a normal total diffusing capacity, indicates that reversible functional changes during hyperventilation on exercise may be a more important cause of disability than structural diminution in the capillary bed.

Summary

The clinical, radiological, and physiological characteristics of seven patients with increased transradiancy of one lung are described.

The patients all complained of dyspnoea on exertion. Diminished breath sounds and a hyperresonant percussion note were found over the affected lung. All but one of the patients gave a history of "pneumonia" in earlier life.

Radiographic studies revealed impaired expiratory deflation and decreased hilar and peripheral vascular shadows on the affected side. These changes were observed most often in the middle and lower zones of the right lung.

The physiological defect was distinguishable only in degree from that observed in generalized emphysema. The relatively greater impairment of mixing efficiency in the unilateral disease is attributed to a gross disparity in the rate of ventilation of the two lungs. The normal values obtained for diffusing capacity in five of the seven patients suggests that the unaffected portions of the pulmonary capillary bed had successfully accommodated the increased blood-flow diverted to them. In one patient studied by bronchospirometry, hyperventilation resulted in over-inflation and temporary suspension of oxygen uptake on the affected side.

It is suggested that transient bronchial obstruction in the course of a respiratory infection in earlier life may have been responsible for the changes observed in some of these patients.

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RESPIRATORY OBSTRUCTION IN HAEMOPHILIC PATIENTS

BY

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The dangers of bleeding from external wounds in haemophiliacs are well known; bleeding into the muscles, joints, urinary tract, and gastro-intestinal tract also produces syndromes that are well recognized and have been the subject of many articles. A less common condition, but of far greater immediate danger to the patient, is the extravasation of blood into the tongue, the tissues of the floor of the mouth, and the fascial planes which surround the pharynx, larynx, and trachea. Haemorrhage here can produce gross swelling of the tissues with consequent encroachment on the space within the mouth and the pharyngeal and laryngeal air-passages. At best the patient suffers some degree of discomfort, with difficulty in speech and dysphagia; and, where very gross distortion of the tissues occurs, there is grave risk of death from asphyxia. Biggs and Macfarlane (1957) regard this complication as the most dangerous than can occur in haemophilia.

Numerically the problem is small, since it is estimated that the haemophilic population of this country is only 2–3 per 100,000. However, it can occur in other conditions that are characterized by a haemorrhagic diathesis: one case in the series under review was in a patient suffering from Christmas disease. Judging from reports in the literature, the syndrome is not common amongst known haemophiliacs. I can find records of only 21 such patients, of whom 16 suffered from some degree of respiratory embarrassment. These were reported by Umbreit (1910), Feliciangeli (1921), Lesné *et al.* (1921), Dujarier (1930), Troutt (1931), Voit and Paus (1933), Endicott *et al.* (1942), Baird and Fox (1943), Fox *et al.* (1946), Davidson *et al.* (1949), Boyd (1950), Herson (1950), Edmonds (1951), MacDonald *et al.* (1953), Tempest (1953), Perrella and Costa (1954), Archer and Zubrow (1954), and Skolnik and Fornatto (1955).

Twelve further instances are described in this paper, and their management is discussed, with particular reference to the assistance that the anaesthetist may be called upon to give. Between 1953 and the end of 1958 79 patients with haemophilia were admitted to the United Oxford Hospitals; as several were admitted on more than one occasion the total number of admissions was 145. Of these, six suffered in greater or less degree from the syndrome described, and two were admitted twice for the same reason. In addition, three cases are described which were seen at other hospitals—one from the records of the Central Middlesex Hospital and two from St. Bartholomew's Hospital. Respiratory embarrassment severe enough to cause grave anxiety occurred in six patients; in three of these active intervention was needed to restore the patency of the airway. One of the three died.

Case Histories

Case 1

A 3-year-old boy, who had been a known haemophiliac since infancy, developed a swelling behind the angle of the mandible on the right side. There was no history of any precipitating factor. Over the next 24 hours the extravasation of blood extended to the tissues of the floor of the mouth and he had difficulty in eating owing to displacement of the tongue. At this stage he was admitted to hospital. There was no indication that the airway was impaired, and an intravenous drip was set up under rectal anaesthesia (500 mg. of thiopentone). After 400 ml. of fresh frozen plasma had been given in one hour the swelling rapidly diminished in size. He was discharged from hospital two days after admission.

Diagnosis and admission to hospital in this case were carried out before the bleeding had produced any impairment of the airway. As a result, resolution of the condition was accomplished by antihaemophilic treatment alone. Had admission been delayed a further 24 hours the child's condition would have been much more serious.

Case 2

A 9-year-old boy—a known case of Christmas disease—was admitted to hospital with the following history. Five days before admission he complained of a sore throat. He then developed swelling of the right side of his face and neck which gradually increased in size. On the morning of admission he complained of being unable to swallow and was having some difficulty in talking. On examination he had a sublingual haematoma, and some bruising and swelling of the soft palate and the right side of the face and neck. Obviously he was on the verge of acute respiratory obstruction, and an intravenous transfusion was set up at once and 2 pints (1,140 ml.) of fresh frozen plasma was given. The swelling subsided, and in four days had disappeared from within the mouth and the face and neck. Again measures to correct the clotting defect were sufficient to check the process in this patient, but some anxiety about him in the first 24 hours after admission made it essential that his condition was most carefully watched.

Case 3

A 12-year-old boy, a known haemophiliac since infancy, was admitted to hospital with a history that over the previous 24 hours he had developed a swelling under his tongue which was spreading to the tissues on the right side of his mouth. There was no history of any precipitating factor, and though he could swallow fluids he was unable to chew solid food owing to displacement of his tongue. Over the next 24 hours he was watched in the ward, and his condition appeared to be static. Treatment was complicated by his persistent refusal to submit to venepuncture. As there was no impairment of the airway a general anaesthetic was given and a drip set up. Two pints (1,140 ml.) of fresh frozen plasma was given during the next two days, and thereafter the swelling rapidly disappeared.

All precautions (these are discussed later) were taken to deal with obstruction of the airway should this have arisen. Fortunately, no such trouble occurred, and the administration of an inhalational anaesthetic presented no difficulty.

Case 4

This patient, a known haemophiliac, was admitted on two separate occasions for bleeding in the area of the tongue and mouth.

On the first occasion, when 7 years old, he bit his tongue, which began to swell, and he was admitted to hospital at once. On admission his tongue was swollen but was not bleeding into the mouth. His swallowing and breathing were unaffected. He was kept under observation in the ward for 24 hours, when it was clear that the condition was resolving without the need of any active treatment; he was then discharged.

A year later he developed a sore throat. One week after the onset a swelling appeared in his neck just below the left ear. During the course of the day this rapidly increased in size and spread down to the angle of the jaw. He had dysphagia and difficulty in speaking. He was at once admitted to hospital, where it was noted that the left side

of his face and neck was swollen and that a haematoma was causing swelling of the tissues of the floor of the mouth, displacing the tongue. Again severe respiratory embarrassment within a few hours was an obvious hazard, and he was transfused with 1 pint (57 ml.) of fresh frozen plasma; a further pint (570 ml.) was given the next day, when the swelling rapidly subsided. He could talk and swallow without difficulty in two days, and was discharged from hospital shortly afterwards.

Case 5

This patient was also admitted on two separate occasions on account of this syndrome. He had been a known haemophiliac since infancy.

On the first occasion, when 5 years old, he developed a haematoma of the floor of the mouth which spread over the chin and affected mainly the right side. He was admitted to hospital, and then developed signs and symptoms of haemarthrosis of the left hip and gastro-intestinal haemorrhage. Antihaemophilic treatment was at once instituted and bleeding from all three sites stopped. In this instance the sublingual haemorrhage caused him little more than mild discomfort, and more anxiety was felt on account of the bleeding from the other sites.

When 18 years old he was again admitted, with the following history. Two days before admission he complained of a sore throat, and the next day of a lump in his throat and hoarseness. Early on the day of admission he suffered from dysphagia, and was at once sent to hospital. On examination there was bruising of the palate, the tongue was swollen and bruised, and there was marked swelling and discoloration of the posterior pharyngeal wall. He was having difficulty in talking, and could not swallow anything. Two pints (1,140 ml.) of fresh frozen plasma were transfused at once, and he was watched carefully for 24 hours. At the end of this time he was comfortable, and the swelling in all areas had decreased. The next day he could talk and swallow with ease.

One other complicating factor in this patient was that he developed an allergic reaction during transfusion of the first pint (570 ml.) of plasma, which produced some oedema of his face. Mepyramine hydrogen maleate, 100 mg., was given into the drip, and a further 50 mg. was added to the second pint. The reaction subsided, and there was no more trouble of such a nature.

Again any further delay in admitting this patient to hospital would have entailed the risk of a serious deterioration in his condition. The risk of an allergic response to plasma, and, even more, antihaemophilic globulin (A.H.G.) obtained from animal sources, is well recognized as a hazard in treating haemophiliacs, and must be controlled with antihistamine drugs.

Case 6

This patient was a 6-year-old boy who was a known haemophiliac. The day before admission he complained of a sore throat, and a few hours later began to bleed from a loose tooth, a lower right bicuspid. During the night, swelling of the floor of the mouth and tongue occurred, and early next morning he was sent to hospital. On examination he could not talk or swallow; the loose tooth was extracted without anaesthesia to allow blood to escape, and he was transfused with 2 pints (1,140 ml.) of fresh blood. It was, however, apparent that his airway was becoming obstructed. As there was no evidence that the obstruction was due to other than the grossly enlarged tongue blocking both the mouth and the oropharynx, it was decided to pass a nasopharyngeal tube. This produced immediate relief of his symptoms, and was left *in situ* for a total of 48 hours. The tube was well lubricated and its passage was carried out without a laryngoscope.

Two pints (1,140 ml.) of fresh frozen plasma was given, and the swelling began to subside. A further 4 pints (2,270 ml.) of plasma was given over the next three days. By then he could talk and swallow normally, and his convalescence was uninterrupted.

Case 7

A 15-year-old boy, a known haemophiliac since the age of 2, had been in hospital for three months, having had an extensive laminectomy for an extradural haematoma caused by a fall. He complained of a sore throat one evening, but nothing abnormal was seen on inspection. Twenty-four hours later his throat was still sore, and some slight external swelling of the left side of his neck was noted. By the next morning the swelling was larger and he was hoarse. By midday he had a marked haematoma of the floor of the mouth and neck, and his respiration was becoming laboured. His haemoglobin was 60%, and 3 pints (1,700 ml.) of fresh blood was given. By the following morning his breathing was much easier and the swelling had subsided slightly. Over the next 24 hours he was given a pint (570 ml.) of fresh plasma and 5 pints (2,840 ml.) of fresh blood. This was followed by a rapid resolution of the condition, and three days later the appearance of his mouth and neck was virtually normal.

Again there was a period of some 24 hours when considerable anxiety was present about his airway. Antihaemophilic treatment alone was sufficient to effect a complete recovery.

Case 8

This patient, who was admitted to the Central Middlesex Hospital, was the subject of an article by Joules and Macfarlane in 1938, though their interest lay in the extreme rarity of the condition. She was, in fact, a woman in her late fifties, suffering from pseudo - haemophilia, who bled into her tongue without obvious cause, and was admitted to hospital with a grossly enlarged and discoloured tongue with some swelling of the submental region. Her appearance is shown in Fig. 1, and this demonstrates well the reason for the severe dysphagia of which these patients may complain. No active intervention was called for in this case, and over the next 10 days her condition resolved. Her airway, despite the somewhat frightening appearance, was not in danger.

FIG. 1.—This patient (Case 8) could not close her mouth any further owing to the swollen tongue, the underside of which is seen projecting. Note also the swelling in the submental region.

Case 9

This patient was an 18-year-old youth who was admitted to St. Bartholomew's Hospital in 1937, under the care of the late Dr. G. Evans. He had been a known haemophiliac since infancy. He gave a history of having had a sore throat a fortnight previously which apparently cleared up in four days. The day before admission he complained of discomfort under the left side of his jaw which grew worse, and he found himself dribbling saliva. During the night his tongue became swollen, and by morning he could neither talk nor swallow. On arrival at hospital a large sublingual haematoma was found to be displacing the tongue. Fresh blood was at once given, but the swelling increased throughout the day. His discomfort became worse, and it was clear that respiratory obstruction was supervening. Attempts to pass a tube by mouth and nose without anaesthesia were unsuccessful, as the patient was restless, and it was decided to administer a general anaesthetic and to intubate him before proceeding to an immediate tracheotomy. Just before passage of the tube his pulse suddenly vanished, and, despite resuscitative measures with oxygen and nikethamide, never returned.

The post-mortem specimen is shown in Fig. 2. This shows that respiratory obstruction was due entirely to the displacement of the tongue backwards and upwards. The extravasation of blood into the substance of the tongue and the tissues of the floor of the mouth can also be seen. The appearances of the other organs of the body were those of death from asphyxia.

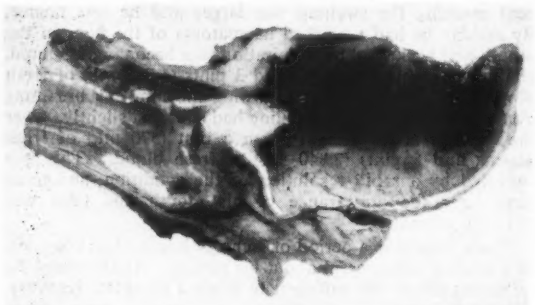

FIG. 2.—Post-mortem specimen, Case 9. Asphyxia was caused by the grossly swollen tongue pressing against the posterior pharyngeal wall. Note that the larynx, apart from the petechial haemorrhages characteristic of asphyxial death, is quite uninvolved in the main pathological condition.

Case 10

This patient was also admitted to St. Bartholomew's Hospital, under the care of Lord Horder in 1935. He was aged 19 years, and had been a known haemophiliac since infancy. Five days before admission he complained of soreness of the gums of the lower jaw, and there was slight bleeding from the gingival margin. Swelling of the submental region began three days before admission. By the time that he arrived at hospital this was very pronounced, there was displacement of the tongue, and the gums of his lower jaw were swollen and discoloured. It was noted that some of his lower molar teeth were grossly carious. His airway at this time was not impaired, but shortly after arriving in the ward respiratory obstruction occurred. This was relieved by passage of a nasopharyngeal tube without the aid of a laryngoscope or of any form of anaesthesia. The tube was left *in situ* for four days, during which time fresh blood was administered to correct the clotting defect. The swelling decreased, and he made a good recovery.

Aetiology

As in all manifestations of haemophilia, only the slightest of stimuli is necessary to start bleeding; indeed, in many cases no precipitating factor can be elicited. In the 12 instances cited, trauma was a factor in one, sore throat in four, in two the cause was related to the dental condition, and in five no cause could be determined. Fox *et al.* (1946) and Davidson *et al.* (1949) state that haemophiliacs must be warned against excessive use of the voice; shouting and similar activity can be a factor in producing bleeding in the tissues around the upper respiratory passages. A further point made by Perrella and Costa (1954) is that the almost continuous movement and muscular activity present in the structures of the floor of the mouth and tongue will encourage bleeding once it has started.

In the cases reported in the literature, trauma as the obvious cause of the haemorrhage is mentioned only by Edmonds (1951). Under this heading must also be mentioned dental treatment in haemophiliacs, and two points must be emphasized in this connexion. The first is the danger of employing local analgesia. This is particularly important in the lower jaw; haemorrhage resulting from inferior dental nerve block or the infiltration of the gum of the lower jaw can easily track into the tissues of the floor of the mouth and tongue. Tempest (1953) and Archer and Zubrow (1954) both report such occurrences. The second is the danger inherent in suturing a bleeding tooth socket in a haemophiliac (Macfarlane and Witts, 1942; Endicott *et al.*, 1942). Such a procedure deprives the blood of its only possible means of escape from the tissues and thus creates ideal conditions for this syndrome to arise. In the United Oxford Hospitals all dental extractions in patients with haemorrhagic diatheses are carried out under general anaesthesia, and the dental and anaesthetic techniques used have been described by Wishart *et al.* (1957) and Leatherdale (1958). The anatomy of the region obviously plays a very important part in determining the path followed by the extravasated blood, and these considerations are fully dealt with by Endicott *et al.* (1942) and by Fuller in the article of Archer and Zubrow (1954).

Treatment

Treatment may be considered under the two following headings.

Specific Antihaemophilic Therapy

This is the province of the haematologist, and no attempt is made to discuss it in any detail here. However, the anaesthetist and all others concerned in the treatment should have some knowledge of the subject, as this will give them a better understanding of the problems involved. For present purposes it suffices to say that the sooner antihaemophilic treatment is instituted and a haemostatically effective level of A.H.G. in the blood thus secured, the sooner will bleeding cease and resolution of the condition begin. This is the primary therapeutic consideration; and all other measures (with which this paper is mainly concerned) are directed towards overcoming any respiratory embarrassment that may arise before the bleeding has been arrested.

Measures to Ensure Maintenance of a Clear Airway

As is seen from the case-histories quoted, the degree to which the airway may be impaired is variable, and it follows that the amount of active intervention necessary to maintain adequate respiration varies from case to case. Experience in the United Oxford Hospitals suggests that certain facts are of great practical importance.

1. The patient should be admitted to hospital at the earliest moment, irrespective of the apparent triviality of the condition when first seen. There is no time or place for expectant treatment in the patient's home. There is the ever-present hazard of death from asphyxia, and, moreover, antihaemophilic treatment can be carried out satisfactorily only in hospital.

2. Care of these patients involves close co-operation between the physician in charge, the haematologist, the ear-nose-and-throat surgeon, and the anaesthetist. Each must be informed when such a case is to be admitted to hospital. The last two should make preparations for any immediate treatment that may be needed to relieve respiratory obstruction; this is discussed in detail later, but the necessary instruments for passage of a pharyngeal or endotracheal tube, and for tracheotomy, must be kept by the patient's bedside so long as there is any danger of asphyxia.

3. Some person (nurse or doctor) who is fully conversant with the dangers must be at the patient's bedside continuously while the slightest risk of respiratory obstruction exists. Every breath must be seen or heard.

4. As in the nursing of unconscious patients, the supine position is to be avoided. The lateral or semi-prone position helps to keep a congested and swollen tongue away from the posterior pharyngeal wall. A rubber airway, such as Guedel's, well lubricated with local analgesic, may be of assistance. A metal airway should not be employed, owing to the danger of producing further trauma.

5. If obstruction to respiration has become established then some means of by-passing it must be performed. Fig. 2 shows the mechanism causing the obstruction, and four methods of relieving are available: (i) orotracheal intubation, (ii) nasotracheal intubation, (iii) nasopharyngeal intubation, and (iv) tracheotomy.

6. Incision and drainage of the collection of extravasated blood has been reported as a means of reducing the swelling and thus relieving the airway (Umbreit, 1910; Feliciangeli, 1921; Troutt, 1931; Edmonds, 1951; Tempest, 1953; MacDonald *et al.*, 1953). Most of the objections to tracheotomy—continuing bleeding, sepsis, and delayed healing—apply here, too. It has not been necessary in any of the cases admitted to the United Oxford Hospitals. It should not be regarded as a substitute for the institution of antihaemophilic treatment; recent advances in this field have rendered the procedure obsolete.

Methods of Relieving Obstruction

Orotracheal and Nasotracheal Intubation

Boyd (1950) reports a case where the former method was employed under general anaesthesia, and MacDonald *et al.* (1953) one where the latter method was used with local analgesia. The endotracheal tubes were left in 96 and 36 hours respectively and both patients made a good recovery. There are certain objections to these procedures. First, general anaesthesia in the presence of respiratory obstruction has long been recognized as notoriously hazardous (Macintosh and Pratt, 1940); Case 9, quoted above, is an example of this. In addition, exposure of the glottis and the passage of an endotracheal tube via the nose or mouth may well be extremely difficult in such distorted anatomical conditions whatever method of anaesthesia is employed. Such manœuvres also carry the risk of producing yet more trauma and bleeding. This method is not recommended.

Nasopharyngeal Intubation

In the two patients quoted (Cases 6 and 10) where passage of a tube was necessary to by-pass the obstruction a nasopharyngeal tube proved very satisfactory. There is no need for the assistance of a laryngoscope, and, provided that the lower end of the tube lies beyond the site of obstruction produced by the swollen tongue and floor of the mouth, there is no need to advance it further. Haemorrhage from the nasal mucosa is an obvious risk, but this is minimized if the following points are adhered to. Spraying the nose with 5% cocaine will cause vasoconstriction of the mucosal vessels as well as local analgesia; the tube must be no larger than will pass easily through the nose and it must be well lubricated with local analgesic ointment. Once it is in position, patients tolerate its presence without complaint, particularly if it is relieving their asphyxial symptoms. Should bleeding occur the patient must be postured to allow drainage from the nose; it will soon be brought under control by the institution of antihaemophilic treatment.

Tracheotomy

Tracheotomy is the most certain method of relieving respiratory obstruction occurring at or above the level of the glottis, but the operation has very special hazards in the haemophiliac. Bleeding at the actual operation is unlikely to be excessive, but, unless adequate haemostasis is assured, a steady persistent ooze is likely to start some hours post-operatively. This greatly delays healing, and blood may be inhaled or track into the mediastinum. The ultimate success of the operation depends on adequate haemostasis, which can be achieved only by using animal A.H.G. Fresh plasma transfusion will usually arrest and reduce a haematoma but will never be sufficient for operation. Thus, if operation is decided on, animal A.H.G. must be obtained as a matter of great urgency. It is not necessary further to endanger the life of an asphyxiating patient by delay in waiting for supplies of A.H.G., but since it can be obtained within a few hours, treatment can at least be started early in the post-operative period.

An analysis of cases reported in the literature shows that of seven patients who were submitted to tracheotomy, four died; while in 14 where no tracheotomy was performed only two died. Too much importance should not be attached to these figures, as the high mortality in tracheotomized patients might well have been due to too long a delay in relieving obstruction and to the operation having been carried out on a moribund patient. In addition, many patients who did not have a tracheotomy suffered only mild local discomfort. There was never any question that the airway was anything but patent, and, since the risk of asphyxia did not materialize, there was never any indication for tracheotomy.

As the operation of tracheotomy in a haemophilic patient is one which should not be undertaken lightly the indications for carrying it out should be clarified. Haemophilic patients with haematoma giving rise to the syndrome under discussion may be divided into two categories according to the acuteness and degree of anatomical distortion present:

1. Those with a slowly developing haematoma which has been present for 6–12 hours and which is not known to be regressing. These patients should be given immediate treatment with fresh frozen plasma. But an E.N.T. surgeon and anaesthetist should see the patient, and all equipment for relieving respiratory obstruction by passing a tube or tracheotomy should be at the bedside.

2. Patients in whom the haematoma has continued to enlarge despite the treatment suggested above and in whom some degree of respiratory obstruction has developed; also patients seen for the first time with respiratory obstruction. This category can be considered under two headings.

(*a*) Those patients in whom relief of the obstruction is afforded by the passage of a nasopharyngeal tube. Further antihaemophilic treatment should also be given, and the haematologist should try to find out why the original treatment was ineffective.

(*b*) Those in whom obstruction is not relieved by intubation. In these patients an immediate tracheotomy is essential. There can be no excuse for allowing a patient to die an asphyxial death through failure to attempt the operation despite the known dangers. Early diagnosis and adequate antihaemophilic treatment before there is any question of respiratory embarrassment should eliminate the need for tracheotomy, and it is suggested by experience in the United Oxford Hospitals that these factors are the most important ones in determining the management of these patients. In

none of the cases quoted was there an interval of less than 12 hours between the first symptoms and the onset of respiratory discomfort (often it was much longer). Since adequate antihaemophilic therapy should reverse the swelling in 6 to 12 hours, the first 24 hours should allow time for assessment of the airway and the making of a decision on what measures are needed to ensure free respiration. This decision, which must be made on purely clinical grounds, may well be very difficult.

One further point must be made here—namely, if the haematoma involved the larynx *ab initio*, as a result of direct trauma (Edmonds, 1951). Here obviously there is no alternative to immediate tracheotomy.

Summary

The syndrome arising from bleeding into the tongue, floor of the mouth, and adjacent tissues in haemophiliacs is described.

The aetiology and treatment of the condition, with particular reference to the risk of asphyxia and the role that the anaesthetist may be asked to play in the treatment, are discussed.

Twelve further instances of the syndrome, in 10 patients, are described.

Of these, one patient died, two patients required nasopharyngeal intubation to overcome respiratory obstruction, seven cases resolved with antihaemophilic treatment alone, and two required no therapy beyond a short stay in hospital for observation to ensure that spontaneous resolution was taking place.

I am indebted to Dr. P. C. Mallam, Dr. H. L. Ellis, and Dr. V. Smallpeice, of the United Oxford Hospitals, for permission to quote from the records of cases admitted under them; to Dr. E. R. Cullinan and Dr. W. J. Hanbury, of St. Bartholomew's Hospital, for allowing me to make use of the records of two cases; and to Dr. H. Joules, of the Central Middlesex Hospital, for the same facilities in one case. I thank Professor Sir Robert Macintosh, Dr. R. G. Macfarlane, and Dr. Rosemary Biggs, of the haematology department of the United Oxford Hospitals, for much valuable help and criticism; and Miss A. J. Arnott for the drawing.

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STAPHYLOCOCCAL INVASION OF PULMONARY INFARCTS

BY

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Hospital patients run an ever-increasing risk of acquiring secondary staphylococcal infections. These infections are often resistant to antibiotics, for resistant strains may possess increased invasive powers (*Lancet*, 1959). The seriously ill patient has little resistance to staphylococcal invasion, and this added insult may well prove fatal. We have been impressed by the peculiar liability of patients with pulmonary infarction to develop secondary staphylococcal lung infections. Four such cases, seen in a period of 12 months, are described to increase awareness of this complication.

Illustrative Case Reports

Case 1.—A man aged 57 was admitted to the Central Middlesex Hospital on March 14, 1958, with an infarction of the left lung base which followed a superficial venous thrombosis of the right calf. He improved with anticoagulant treatment, and a week's course of penicillin and streptomycin. On March 23, two days after the end of the first antibiotic course, fever recurred and the temperature rose to 104° F. (40° C.). The sputum became purulent for the first time, and *Staph. pyogenes*, sensitive only to chloramphenicol and erythromycin, was isolated from sputum and stool. He was treated with these antibiotics, but for several days was critically ill with delirium and stupor. The blood-pressure fell to 90/70 mm. Hg, and he received intravenous hydrocortisone for five days. A chest radiograph at the height of his illness showed a massive

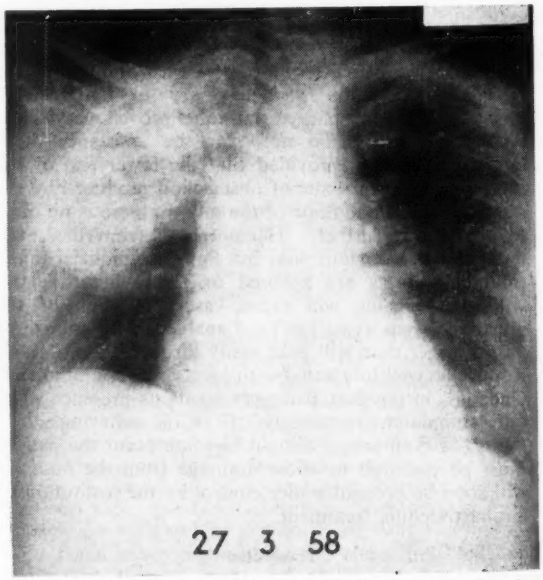

FIG. 1.—Case 1. Chest radiograph showing a massive shadow in the right upper zone.

shadow in the right upper zone, presumably resulting from an infected infarct (Fig. 1). Later, breakdown occurred in this area, with the development of a large cavity (Fig. 2). The sputum was free of pathogens on April 21, and antibiotics were stopped. The cavity closed gradually, leaving only some bronchiectasis (Fig. 3). He returned to work after 30 weeks, and at the time of writing has only transient purulent bronchitis following upper respiratory infections.

Case 2.—A man aged 69 was admitted to the Central Middlesex Hospital on November 2, 1957, for right lateral meniscectomy and decompression of the right median nerve. These operations were uneventful and he was mobilized with physiotherapy. On November 11 he sustained a right basal pulmonary embolism. He improved initially with anticoagulants, but further pleuritic pain developed at the base of the left lung and also retention of urine. A chest radiograph on December 3 showed an abscess of the right upper lobe (Fig. 4), the site being confirmed by lateral film, and sputum contained *Staph. pyogenes* sensitive only to chloramphenicol and erythromycin. With these antibiotics the abscess cavity closed (Fig. 5). After a period of convalescence a retropubic prostatectomy was performed without complication.

Case 3.—A woman aged 73 was admitted to the Central Middlesex Hospital on October 9, 1958. She had spent the previous year mainly in bed after a left hemiparesis, and on the day of admission developed a pulmonary embolism at the left base. The sputum was at first uninfected, but four days later she became much more ill,

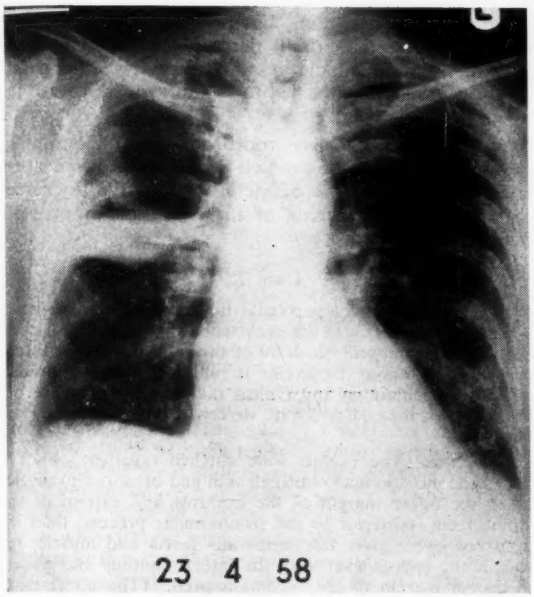

FIG. 2.—Case 1. Showing development of a large cavity.

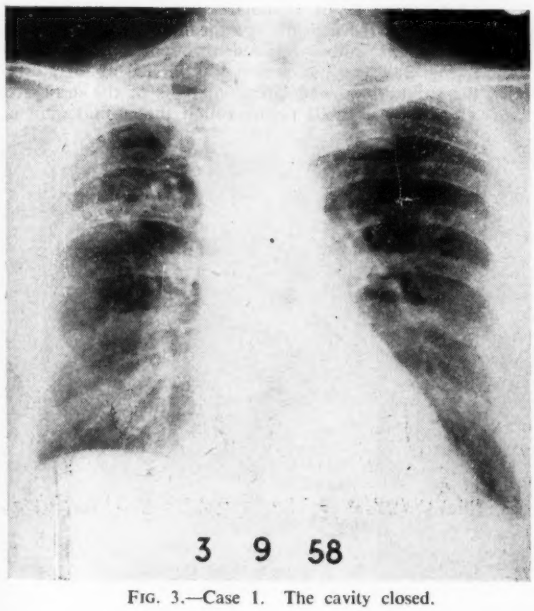

FIG. 3.—Case 1. The cavity closed.

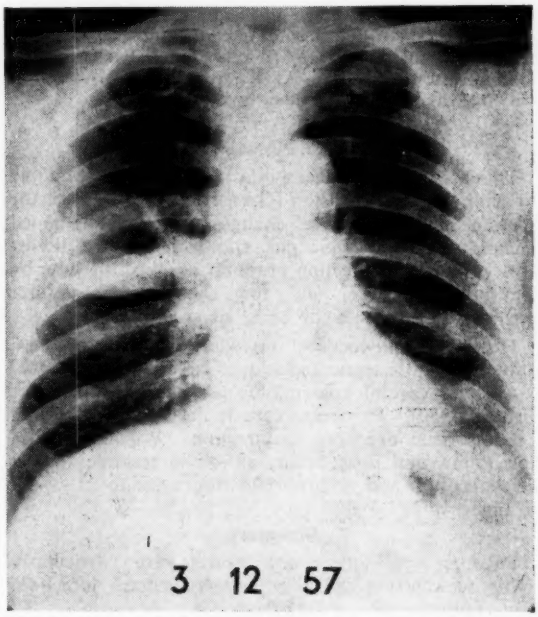

FIG. 4.—Case 2. Radiograph showing abscess of the right upper lobe.

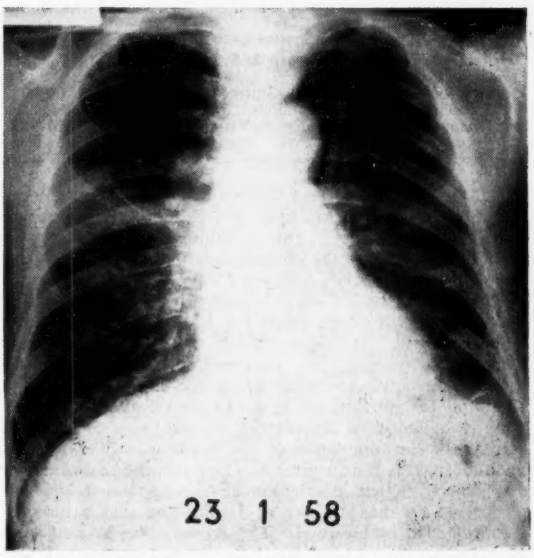

FIG. 5.—Case 2. Abscess cavity closed after antibiotic treatment.

with fever. She was then coughing up purulent sputum containing *Staph. pyogenes* resistant only to penicillin. She slowly improved with chloramphenicol and later tetracycline. Repeated aspiration of a left pleural effusion was necessary.

Case 4.—A woman aged 70 was admitted to Addenbrooke's Hospital, Cambridge, with a fracture of the neck of the right femur. She was treated by the insertion of a nail into the fractured bone. Seven days after operation she had an attack of dyspnoea; several further attacks occurred during the next week. At the end of this time she became pyrexial—temperature 104° F. (40° C.)—and rapidly deteriorated, dying in 48 hours. Necropsy revealed thrombi in the veins of the injured leg and in the pulmonary artery and its branches. Several infarcts were present in the lungs. The largest, in the right lower lobe, occupied about one-third of the lobe and had a soft grey-red central area, which on histological examination proved to be an abscess within an area of infarction. Bacteriological examination revealed *Staph. pyogenes*, type 75, sensitive only to chloramphenicol and erythromycin.

Discussion

Patients with pulmonary infarcts are very susceptible to staphylococcal invasion (Gresham, 1958). When the sputum in such a case changes from blood-stained mucus to haemorrhagic pus, staphylococci are almost always present. Infection probably reached the lung by the bronchial tree, and the haemorrhagic infarct provides an ideal site for bacterial growth.

Hospital staphylococcal infection can be prevented only by rigid aseptic technique, isolation of infected cases, and careful epidemiological study (Ministry of Health, 1959). Particular care is needed to protect ill patients from exposure to infection. When staphylococcal invasion does occur, antibiotic treatment must be energetic and appropriate for resistant hospital strains.

Summary

Patients with pulmonary infarcts are particularly liable to contract secondary staphylococcal infection. Four recent cases are described.

We are grateful to the physicians and surgeons of the Central Middlesex Hospital and Addenbrooke's Hospital for permission to report these cases.

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The Queen's Institute of District Nursing has announced the approval by the Minister of Health of its courses of district-nurse training. The syllabuses of training now available incorporate the recommendations laid down in the Report of the Minister's Advisory Committee on the Training of District Nurses. Centres training under the auspices of the Institute will adopt either the four-months or the six-months course. Students taking either course will, on successfully passing the examination, qualify for the national certificate to be issued by the Ministry of Health as well as for appointment to the Queen's Roll. To achieve a national standard of district nursing was one of the reasons for the foundation of the Institute in 1887, and the Institute regards it as a great step towards the realization of this objective that district-nurse training has now been recognized by the Ministry of Health and that a national certificate will be awarded. Details may be obtained from the Institute at 57, Lower Belgrave Street, London, S.W.1.

DUMB-BELL-SHAPED DERMOID CYSTS OF THE ORBIT

BY

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Harvey Jackson (1951) states that the incidence of dermoid cysts in proved orbital new formations is 6.3%. The majority appear in the upper half of the orbit, more commonly the upper temporal quadrant. The cyst slowly increases in size, eventually to erode the roof of the orbit, to become closely stuck to the bone, and to be in contact with the dura, but rarely adherent to it or invading it. Some orbital dermoid cysts extend into the anterior and middle cranial fossae, into the nasal cavity, and may be attached to the optic-nerve sheath in the apex of the orbit.

When the dermoid has eroded bone the radiographic changes are diagnostic; a well-defined translucent area is surrounded by bone of increased density. In some cases there is broadening of the fronto-malar process (external angular process).

Case 1

Two clinical facts of particular interest about the patient, a young male, are: (1) the recurrence of the dermoid cyst in the upper temporal quadrant of the right orbit after three previous operations to excise it, and (2) the anatomical difficulty in obtaining any typical radiographic evidence of its extension through a 5-mm. defect in the lateral wall of the orbit.

Operation.—The eyelids were stitched together. Fig. 1 shows the incision made through skin and orbicularis muscle along the upper margin of the eyebrow and carried down about 1 cm. posterior to the fronto-malar process, then in a curved sweep over the temporalis fascia and muscle, to end in the crease level with the lateral canthus and along the upper margin of the zygomatic arch. (The upper part of this incision is placed a little lower than that recommended by Dickson Wright (1948) for combined lateral and transfrontal orbitotomy.) The orbicularis muscle was undermined on both sides of the incision and the flaps thus made were retracted by silk sutures passed through the orbicularis muscle (Fig. 2). The periosteum was incised about 3 mm. from the supraorbital and lateral margins of the orbit and was reflected by a small rugine round the orbital margin,

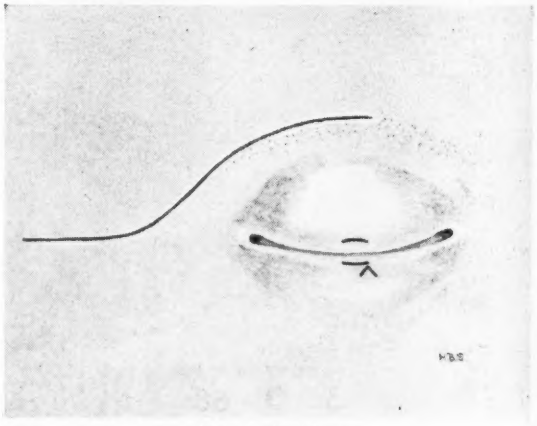

FIG. 1.—Incision.

where it was closely attached. From this point the orbital periosteum was readily separated from the bone with a flat lacrimal dissector (Stallard's).

The temporalis fascia was incised along the posterior edge of the fronto-malar process and the malar bone, and the temporalis muscle was cut antero-posteriorly for about 1.5 cm. at the anterior part of its origin to facilitate its reflection posteriorly. The dermoid cyst in the orbit was dissected and found to communicate through a defect of 5-mm. diameter in the lateral orbital wall with an extension

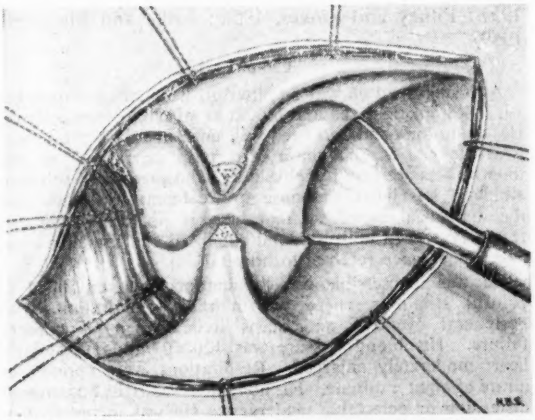

FIG. 2.—Exposure of dumb-bell dermoid cyst of the right orbit and temporal fossa. Partial resection of the lateral orbital wall to show the waist of the dumb-bell, which passed through a 5-mm. diameter erosion in the lateral orbital wall.

of the dermoid cyst in the temporal fossa, deep to the temporalis muscle. The opening in the lateral orbital wall was on a level with the temporal fossa; because of its site and its small size it must have escaped detection at the three previous operations. It was through this aperture that the cyst recurred in the orbit.

A wedge-shaped piece of the lateral orbital margin was removed down to the bony aperture and the full extent of the hour-glass dermoid was exposed (Fig. 2). There was no evidence of extension into the middle cranial fossa or through the roof of the orbit. The cyst was excised completely. The wedge of excised bone was replaced and secured by two 20-day chromic-catgut sutures passed through small drill-holes in either side of each bone-cut.

The skin-muscle incision was closed in two layers. There has been no recurrence 10 years after operation.

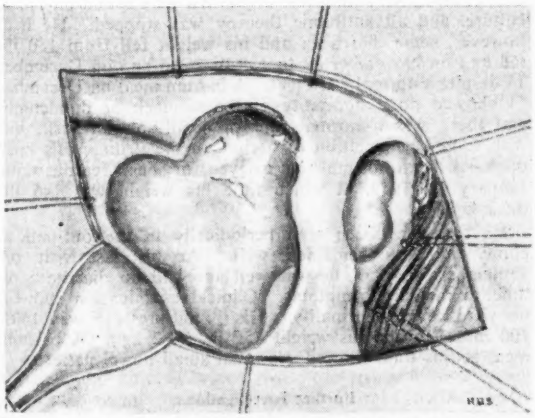

FIG. 3.—Dermoid cyst of the left orbit. Erosion of roof of orbit, lateral part of supraorbital margin, and extension through lateral orbital wall into temporal fossa.

Case 2

Fig. 3 shows a dermoid cyst in a woman, aged 33, which eroded the roof of the orbit, destroyed the supraorbital margin, making a gap 18 by 10 mm., and extended into the temporal fossa through a defect 10 by 5 mm. in the lateral orbital wall beneath the fronto-malar process (external angular process). Three small flakes of bone remnants of the orbital roof were present on the anterior and upper surface of the dermoid cyst. The cyst was in contact with dura but not adherent to it. The remarkable fact in this case was the destruction of the thick supraorbital margin by the insidious pressure of the growing cyst.

Literature

Harvey Jackson (1951) mentions a patient with a dermoid cyst in the temporal fossa and a circular defect in the lateral orbital wall.

Carey (1958) has described the case of a woman aged 51 with a sinus below the lateral canthus. There were a small circular opening in the lateral orbital wall, a dumb-bell-shaped dermoid cyst, and some erosion of the roof of the orbit and temporal fossa exposing intact dura covering the frontal and temporal lobes of the brain. Carey packed the wound with ribbon gauze soaked in 1:80 carbolic acid and allowed it to granulate.

Summary

The features of particular interest in these two cases of dermoid cyst of the orbit are, in Case 1, the recurrence of the cyst due to its extension through a small opening in the lateral orbital wall into the temporal fossa being overlooked, and, in Case 2, the insidious erosive power of these cysts, which are capable of destroying bone as thick as the supraorbital margin.

I thank Dr. W. Darley and the late Mr. Martin Jones for their kindness in referring these patients to me.

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"It is reasonably certain that coronary atherosclerosis has not increased during this century in England at the same rapid rate as has coronary thrombosis, which was certainly rare 50 years ago. Sir William Osler wrote in 1910 that he did not see a case of angina pectoris until after he had been admitted to the Fellowship of the Royal College of Physicians, and he saw no case during ten years of practice in the Montreal Central Hospital. In our country and North America ischaemic heart disease is now the commonest single cause of death, and there are possibly about half a million patients in this country now. My own interest in coronary heart disease dates from a quarter of a century ago when, as a medical student, I was intrigued by the failure of medical science to do much to prolong the lives of middle-aged men. Their expectation of life in England and Wales was only some three years less a century ago than now, despite the great advances in medical science. In the U.S.A. also the expectation of life 60 years ago was only four years less than now. But the diseases that now kill middle-aged men are quite different from those of a century ago when tuberculosis and pneumonia were common, and chronic degenerative diseases such as cardiovascular disease and cancer were rare. I believed that the only environmental factor causing this increase in chronic degenerative disease must be diet, and I was keen to obtain evidence for the dietary factor which seemed likely to be an alteration in trace elements or particular fats. . . ." ("Nutrition and Cardiovascular Disease": address to the Royal Society of Health by Dr. H. M. Sinclair (reader in human nutrition, Oxford University).)

ACUTE ENTERITIS WITH TEMPORARY INTESTINAL MALABSORPTION

BY

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AND

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Increased clinical interest and improved methods of study have demonstrated in recent years that defects in alimentary absorption may occur in patients who do not present the clinical picture of advanced alimentary insufficiency represented by the sprue syndrome. It has also been shown that these defects may be found to a greater or less degree in a variety of diseases, which include biliary obstruction, pancreatic insufficiency, abdominal reticuloses, mesenteric vascular disease, and enteropathies such as regional enteritis and coeliac disease. It would seem reasonable that impairment of small-bowel function might occur in association with acute gastro-enteritis, but this has not been fully documented and few reports of such cases could be found in the literature available to us.

The occurrence of potassium depletion after diarrhoea has been reported by several observers, and it has also been shown that increased faecal loss of potassium is frequent in the malabsorption syndrome (Comfort *et al.*, 1953; Cooke, 1957). These observations refer to chronic alimentary insufficiency with prolonged diarrhoea, but there are also occasional case reports suggesting it may complicate acute episodes. Achor and Smith (1955) reported the case of a man aged 51 who developed hypokalaemia and muscle degeneration after an acute episode of diarrhoea and vomiting. Investigation of this case revealed steatorrhoea and oral and intravenous glucose-tolerance tests suggesting impaired alimentary absorption. These returned to normal on his eventual recovery. Achor and Smith could find no such case in the literature, though the one described by Ariel (1954) might possibly have been similar. Two other relevant cases have both been associated with some congenital abnormality of the spleen. Alexander (1958) described the case of a man aged 72 with congenital absence of the spleen who developed chronic enterocolitis with steatorrhoea after an infection with *Salmonella tennessee*, and Zelman and Lewin (1958) reported the case of a 25-year-old man with intestinal malabsorption, hypogammaglobulinaemia and multiple congenital anomalies, including a right-sided spleen. In this patient the radiological appearances of the bowel became normal after cessation of the diarrhoea.

In children, fat-absorption amounts to 85–90% of the oral intake, and this figure may fall to 60% or less in the presence of diarrhoea. There is also evidence that amino-acid absorption curves show temporary depression in infants after acute gastro-enteritis (Bate and James, 1956).

Mention must also be made of the experimental studies of Reynell and Spray (1958), who found that rats with an enteritis due to castor oil or mercuric chloride solution had defective absorption of glucose and iodide by the small intestine, independent of changes in motility.

The present paper reports two cases which provide some evidence that severe acute enteritis in adults may be followed by a transient phase of intestinal malabsorption of considerable clinical significance. The laboratory methods used have been discussed elsewhere and do not require further description (Benson *et al.*, 1957; Pitney and Stokes, 1958; Joske and Blackwell, 1959).

Case 1

A farmer aged 66 was admitted to hospital on November 19, 1958, disorientated and in a state of circulatory collapse. He lived alone and had been well until five days previously, when he had a rapid onset of copious diarrhoea. At this time he was seen by his physician, who prescribed sulphonamides. His initial response to treatment was good and the diarrhoea ceased, so that he was not seen again for four days, when he was found collapsed and semicomatose, and was at once referred to hospital.

He was inaccessible on examination, but responded to painful stimuli. There was marked dehydration, with peripheral cyanosis and stasis indicative of circulatory failure. His blood-pressure was 120/60 mm. Hg and his heart moderately enlarged. Respirations were periodic at a rate of eight a minute. His abdomen was rigid but without distension or detectable tenderness. He was incontinent of faeces.

Initial investigations confirmed the clinical impression of infection and fluid and electrolyte depletion: haemoglobin, 13.8 g./100 ml.; white-cell count, 21,100/c.mm., with a polymorphonuclear leucocytosis; serum Na, 107 mEq/l.; serum K, 4.9 mEq/l.; blood sugar, 136 mg./100 ml.; blood urea 268 mg./100 ml.; serum albumin, 2.8 g./100 ml.; serum globulin, 2.7 g./100 ml. Stool cultures at this time grew a *Salmonella* group B organism.

Treatment was begun on admission with intravenous fluid and electrolyte replacement and parenteral tetracycline, 250 mg. six-hourly. Despite intensive therapy, however, adequate hydration was not achieved for two days. During this time he remained disorientated, with slow irregular respirations, and an area of gangrene developed on the tip of his tongue. Five days after admission he experienced abdominal distension and retention of urine: his serum potassium was found to be only 2.9 mEq/l. Parenteral potassium supplements were increased to 200 mEq daily, and thereafter he slowly but steadily improved. After three weeks in hospital he was rational and continent and was eating well. No pathogenic organisms were found on faecal culture, and all antibiotic therapy was stopped. He had, however, some diarrhoea and his weight fell from 150 lb. (68 kg.) on November 29 to 138 lb. (62.6 kg.) on December 13 despite a normal ward diet. A barium meal on December 11 showed no abnormality of the stomach or duodenum, and there was a normal rate of small-bowel transit, but with some segmentation of barium in the ileum. His final discharge from hospital was delayed for social reasons until January 12, 1959, at which time his weight was 146 lb. (66.2 kg.).

He has since been seen periodically in the out-patient clinic, and has remained well. At his last visit on September 30, 1959, he was well and had no diarrhoea or other alimentary symptoms. Clinical examination showed no significant abnormality. His blood-pressure was 160/100 mm. Hg and his weight 157 lb. (71.2 kg.). A barium meal at this time showed a normal small-bowel pattern.

Further Investigations

This patient was well, without symptoms of alimentary disease and maintaining a constant weight, until he had an acute illness with diarrhoea followed by circulatory collapse.

At this time *Salmonella* group B organisms were recovered from his faeces. There is thus strong clinical and bacteriological evidence that he was suffering from acute bacillary dysentery. After this acute illness he continued to have some diarrhoea and to lose weight, while a barium meal showed a "malabsorption pattern" in his small bowel. Further investigations of alimentary function were therefore undertaken during his convalescence, and these provided additional evidence of a temporary absorption defect with eventual recovery. Some of the results of these investigations are shown in Table I.

TABLE I.—*Biochemical Results from Case* 1, *Showing Temporary Depression of Protein, Lipid, and Calcium Levels, With Later Return to Normal*

Date	Serum Albumin (g./100 ml.)	Serum Globulin (g./100 ml.)	Plasma Carotene (µg./100 ml.)	Serum Cholesterol (mg./100 ml.)	Blood Urea (mg./100 ml.)	Serum Calcium (mg./100 ml.)	S.G.O.T. (Units)	Serum Amylase (Units)
20/11/58	2·8	2·7	—	—	268	6·6	—	420
24/11/58	2·4	3·0	87	136	310	—	53	227
2,3/12/58	2·4	3·5	—	—	43	9·2	41	196
15/12/58	2·5	3·8	79	—	—	8·9	—	—
29/12/58	2·9	3·5	—	—	32	9·9	—	307
8/1/59	3·2	3·3	—	—	—	10·5	13	207
28/1/59	4·1	3·6	200	—	—	—	—	228
24/3/59	4·2	3·5	166	256	40	—	—	—

Electrolyte Metabolism.—The initial electrolyte picture was of gross electrolyte depletion with acidosis. Treatment of this brought a progressive fall in serum potassium from 4.9 mEq/l. on admission to 2.7 mEq/l. five days later. However, as the patient was incontinent of urine and faeces, no measurements of electrolyte content of urine or faeces were possible. The high blood urea which returned rapidly to normal was probably also a manifestation of fluid and electrolyte depletion (Table I).

Haematological Studies.—Defective absorption of vitamin B_{12} was demonstrated on two occasions. With an oral dose of 0.6 µg. ^{58}Co-vitamin B_{12} (Pitney and Stokes, 1958) there was a urinary excretion of 1.4% of the ingested dose on December 19, 1958, and of 2.4% on January 6, 1959. When the tests were repeated with 50 mg. of intrinsic factor, the corresponding results were 19.3% and 27.6% respectively, which are within the normal range.

These results show an intrinsic-factor deficiency of the pernicious-anaemia type, and their explanation is uncertain. It may be either that the patient had in fact subclinical pernicious anaemia or that the results represent the absorptive defect which may follow severe infection of any type.

Fat-Absorption.—Defective fat-absorption was shown by a six-day fat balance from December 13 to 18. With a fat intake of 80 g. daily, faecal excretion was 5.8 g./day as stearic acid. There were also low plasma levels of carotene and cholesterol, which returned to normal during succeeding months (Table I).

Protein Absorption.—Abnormal protein absorption was suggested by a low serum albumin level on admission with a later return to normal (Table I). There is no evidence of whether this represents a true absorptive defect or an acute protein-losing enteropathy associated with the acute enteritis (Gordon, 1959).

Carbohydrate Absorption.—The D-xylose absorption test was performed on three occasions before the patient was discharged from hospital. On two of these, five-hour urinary excretion figures of 1.1 and 1.9 g. indicated impaired carbohydrate absorption. The other test gave a normal five-hour urinary excretion of 5.8 g.: the explanation of this result is unknown.

Other Data.—There was a low serum-calcium level on admission (Table I), which was accompanied by a serum inorganic phosphate of 15.2 mg. P/100 ml. Both of these rapidly returned to normal, and were therefore regarded as a reflection of disturbed renal function rather than of alimentary disorder. Conventional liver-function tests were normal on all occasions. Transient increases in serum amylase and glutamic oxalo-acetic transaminase probably reflected temporary pancreatic damage during the acute phase of the illness.

Case 2

A male pensioner aged 75 was admitted to hospital on September 25, 1958, for investigation of generalized muscular weakness. He had been well until two weeks previously, when he developed diarrhoea which had persisted until two days before admission. This was not excessive, however, and he did not seek medical advice at this time. On the day of admission he suddenly became unable to move his legs or to sit up in bed. Because of these symptoms he consulted his family physician, who referred him immediately to hospital.

Examination showed him to be an elderly man with an obvious Parkinsonian tremor. His temperature was normal and his blood-pressure 170/100 mm. Hg. His heart was slightly enlarged, with a grade 1 systolic ejection murmur at the apex, and his peripheral vessels were somewhat thickened and tortuous. His abdomen was grossly distended but soft and not tender to palpation, and occasional high-pitched borborygmi were audible. Examination of the nervous system showed gross diminution of muscular power and tone, with absent deep tendon reflexes in the legs. The plantar responses were both flexor. There was some weakness of the muscles of the back. In the upper limbs power was moderately diminished and the tone increased. The tendon reflexes were present, equal, and brisk. Cranial nerves and sensory system showed no abnormality.

Initial investigations showed severe hypokalaemia: haemoglobin, 13.4 g./100 ml.; white-cell count, 11,200/c.mm., with a polymorphonuclear leucocytosis; serum Na+, 140 mEq/l.; serum K+, 1.9 mEq/l.; serum Cl^-, 94 mEq/l.; serum HCO_3^- 30 mEq/l.; blood urea, 240 mg./100 ml.; serum albumin, 2 g./100 ml.; serum globulin, 4.4 g./100 ml. Electrocardiogram; prolongation of the P-R interval, depression of the ST segments, and a well-defined U wave, consistent with hypokalaemia. A plain *x*-ray film of the abdomen revealed gross gaseous distension of small and large bowel, with fluid levels; and a barium enema

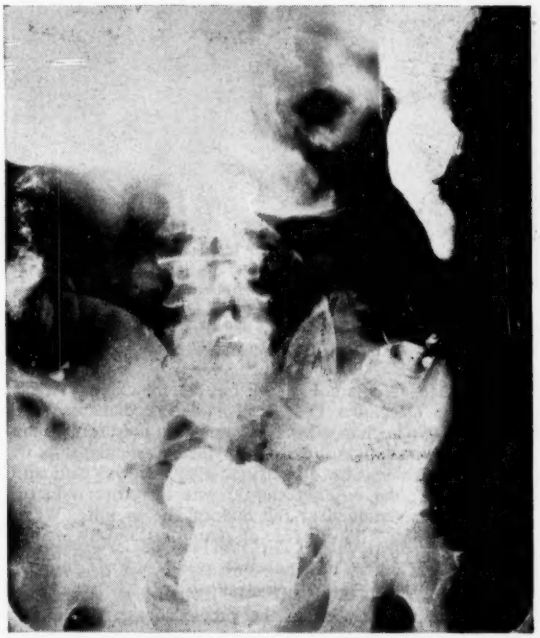

FIG. 1.—Case 2. Barium enema shortly after admission, showing gross dilatation of small and large bowel.

showed the opaque material to enter the dilated loops of colon with ease, excluding a low intestinal obstruction (Fig. 1). Faecal cultures taken at this time grew no pathogenic organisms, but a later specimen showed a moderate growth of *Staphylococcus aureus*, which was treated with antibiotic therapy.

A diagnosis was therefore made of hypokalaemia with neuropathy and paralytic ileus. Treatment was begun with intravenous fluid and electrolyte with added potassium chloride. A total of 980 mEq of potassium was given during the first 40 hours, after which his serum K level was 2.9 mEq/l. These measures were accompanied by clinical improvement, so that further potassium supplements were given orally. However, his diarrhoea recurred two weeks later, and further intravenous therapy was necessary to correct a serum K+ level of 2.1 mEq/l. He was eventually maintained on an oral dose of 160 mEq daily as potassium chloride.

During convalescence further investigation of the cause of his hypokalaemia was undertaken. Radiological and biochemical evidence of intestinal malabsorption was obtained. A barium meal on November 6, 1958, showed the typical flocculation and alterations in luminal calibre of the malabsorption syndrome (Fig. 2). The biochemical

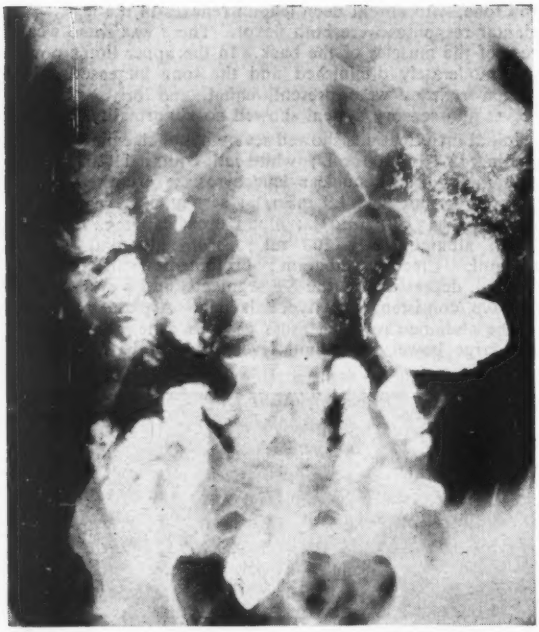

FIG. 2.—Case 2. Barium meal after recovery from the acute phase, showing irregularity of calibre of the small bowel with flocculation of barium sulphate medium.

findings are discussed below. He was finally discharged from hospital on November 29, at which time his weight was 120 lb. (54.4 kg.).

He has been seen since in the out-patient clinic. At his first visit on December 11 he still had some diarrhoea and his weight was unchanged. Treatment was therefore begun with prednisone, 30 mg. daily, and further supplements of potassium chloride. On January 6, 1959, he was well and symptom-free; the dose of steroid was therefore reduced, and it was discontinued at the end of the month. When last seen on May 5 he was free of symptoms and his weight was 163 lb. (73.9 kg.).

Further Investigations

These are presented as in the previous case.

Electrolyte Metabolism.—The clinical picture in this case was that of potassium depletion, and there is considerable evidence that this was due to excessive loss of potassium in the faeces. When on oral potassium chloride supplements the patient had a persistently low urinary potassium excretion from 7 to 25 mEq daily. Faecal potassium excretion was measured on two occasions, values of 120 mEq/day and 110 mEq/day being obtained on October 15 and November 19 respectively. The normal faecal potassium is of the order of 10 mEq/day. Faecal potassium losses of the order of 100 mEq/day in the presence of normal or low serum and urinary levels are strong presumptive evidence of intestinal malabsorption (Cooke, 1957). As in the previous case, the initial elevation of the blood urea is thought to be due to electrolyte depletion and hypokalaemia.

Haematological Studies.—Defective absorption of vitamin B_{12} was present in this patient. On November 14, 1958, a urinary excretion test using 0.6 μg. of ^{58}Co vitamin B_{12} gave a figure of 6.5% of the ingested dose. When this was repeated with 50 mg. of intrinsic factor a value of 14.1% indicated that absorption was still subnormal.

This patient also had a histamine-fast achlorhydria, shown by biopsy to be the result of atrophic gastritis.

Fat-Absorption.—No fat balance was possible in this case, but depressed fat-absorption was suggested by the low levels of plasma carotene and serum cholesterol and total lipids (Table II), all of which increased during the period of observation, though the carotene at no stage reached the lower limit of the normal range (70 μg./100 ml.).

TABLE II.—*Biochemical Results from Case 2, Showing a Depression of Albumin, Cholesterol, and Total Lipid Values Returning to Normal, and a Persistently Low Plasma Carotene Level*

Date	Serum Albumin (g./100 ml.)	Serum Globulin (g./100 ml.)	Plasma Carotene (μg./100 ml.)	Serum Cholesterol (mg./100ml.)	Total Plasma Lipids (mg./100 ml.)	Blood Urea (mg./100 ml.)	Serum Calcium (mg./100 ml.)	Serum Phosphate (mg./100 ml.)
30/9/58	2·0	4·4	—	168	—	241	—	—
6/10/58	2·3	4·0	—	—	—	92	8·7	3·3
13/10/58	2·6	5·2	—	—	—	32	9·4	—
21/10/58	2·4	4·1	—	—	—	151	—	—
11/11/58	2·8	4·2	14	215	310	44	9·5	—
17/11/58	2·8	4·1	—	—	—	—	—	—
11/12/58	4·1	3·8	43	—	—	90	—	—
13/5/59	3·4	3·7	27	253	910	35	9·2	3.3

Protein Absorption.—As in the previous case, there was an initial hypoalbuminaemia, with a later return to normal levels (Table II).

Carbohydrate Absorption.—A D-xylose absorption test on November 13 showed a urinary excretion of only 1.4 g. in five hours, indicating carbohydrate malabsorption.

Other Data.—There was a slight hypocalcaemia on admission but no change in serum inorganic phosphate. Liver-function tests, serum amylase, and glutamic oxaloacetic transaminase were normal on all occasions. Plasma magnesium on one estimation was depressed to a value of 1.5 mEq/l., the normal value for this hospital being 1.9 to 2.5 mEq/l.

Assay of the urine for aldosterone did not show this to be increased.

Discussion

The sequence of events in these patients was similar. Both were well, with no abdominal symptoms and maintaining a steady weight, until the occurrence of an acute episode with the clinical features typical of acute enteritis occurred, leading to an illness severe enough to warrant admission to hospital. In both patients an organism which may cause acute enteritis was cultured from the faeces. This acute diarrhoeal illness was followed by a prolonged period of debility and progressive loss of weight, and laboratory investigations at this stage were highly suggestive of intestinal malabsorption. In Case 1 this was shown by abnormal radiological appearances of the small bowel,

hypokalaemia, impaired vitamin B_{12} absorption, steatorrhoea, hypoalbuminaemia, and depressed xylose absorption. In Case 2 similar radiological appearances occurred, but the clinical picture was dominated by excessive loss of potassium in the faeces, with resultant hypokalaemia. Absorption of vitamin B_{12} and xylose was also impaired, and there was hypoalbuminaemia. Steatorrhoea was not demonstrated in this patient, but the illness was accompanied by low serum cholesterol and plasma carotene levels.

Both patients made a complete clinical recovery and when last seen were without symptoms and had regained their normal weight. In Case 1 this was accompanied by a return to normal of the biochemical parameters, but in Case 2, in which the period of observation was shorter, these improved, but without a complete return to within normal limits.

It is suggested, therefore, that these two patients suffered from a severe acute enteritis which caused enough damage to the small bowel to result in a temporary phase of malabsorption before eventual recovery occurred.

One other possibility must be mentioned—that these patients had latent malabsorption before the acute illness which led to detailed investigation. This cannot be fully excluded; but several facts are against it, notably the patients' apparent state of good health beforehand and the progressive clinical and biochemical recovery which followed the acute diarrhoea. On the other hand an acute enteritis complicating a latent atrophic jejunitis might well explain the clinical and biochemical severity of the illness in our present cases.

If in fact an acute enteritis led to a prolonged phase of intestinal malabsorption, the mechanism of this is uncertain. A similar sequence may follow acute ischaemic episodes in man (Joske *et al.*, 1958), though Cameron and Khanna (1959) have shown experimentally that regeneration of intestinal villi after extensive mucosal infarction is extremely rapid in the rat. It would follow, therefore, that structural mucosal integrity alone is insufficient for normal alimentary function, and that more subtle concepts of tissue organization must be considered. The recent work of Gordon (1958) is relevant to this, and suggests that this post-infectious state may be due to an acute exudative enteropathy rather than to a primary absorptive defect. It is unlikely that the results observed are due to altered intestinal motility, for the available evidence provides little evidence relating absorption to motility. Cummins and Almy (1953) found hypermotility to be associated with increased absorption. Further speculation, however, is not within the province of the present paper.

Summary

Two cases are reported which provide evidence that severe acute enteritis in adults may be followed by a temporary phase of intestinal malabsorption before recovery.

A man aged 66 developed acute bacillary dysentery, and after the acute episode was found to have impaired absorption of fat, carbohydrate, protein, and vitamin B_{12}. This was accompanied by diarrhoea and loss of weight. Both clinical and laboratory abnormalities returned to normal during the succeeding five months, and he has since remained well.

A man aged 75 presented with hypokalaemic neuropathy after an acute episode of dysentery. Investigation showed gross elevation of faecal potassium, and a defective absorption of fat, carbohydrate, protein, and vitamin B_{12}. After the acute episode there was progressive clinical and laboratory improvement.

Since mucosal regeneration in the small bowel is rapid, and prolonged defects of function followed an acute episode, it is suggested that mucosal integrity also is insufficient for normal small-bowel function.

Our thanks are due to Dr. D. H. Curnow and Dr. W. R. Pitney for the laboratory investigations performed in these cases. The urinary aldosterone estimation in Case 2 was made at the Middlesex Hospital, London, through the courtesy of Dr. J. D. N. Nabarro.

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VOMITING BY OUT-PATIENTS AFTER NITROUS OXIDE ANAESTHESIA

BY

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This is an investigation into some of the factors relating to the occurrence of vomiting after the administration of nitrous oxide and oxygen in the casualty department at Hillingdon Hospital. We kept records of 3,000 consecutive anaesthetics given by anaesthetists of not less than registrar status. The patients were not premedicated and no supplementary drugs of any kind were given: the same intermittent-flow apparatus was used throughout. Whenever possible, patients were instructed to attend at least four hours after their last meal.

The following details were recorded: age and sex of the patient; type of operation done; time since the last meal; time of an accident when one occurred; duration of the anaesthetic, from the start of induction until the nitrous oxide was turned off; presence or absence of vomiting within the first quarter of an hour after operation; and the nature and quantity of the vomitus. (For the purpose of this investigation those patients who retched were recorded as having vomited.)

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Findings

A total of 440 patients (14.7%) vomited; but a remarkable variation around this proportion was demonstrated when the results were analysed according to the patient's age, the duration of the anaesthetic, and the type of operation performed.

Age.—When the figures for age were divided into their respective decades (Fig. 1) the highest vomiting rate was found in the first (24.2%). In the third, fourth, and fifth decades the rate was lower, averaging 7.9%; it rose for elderly patients to an average of 12.3%. An analysis by individual years of age showed the highest incidence to be in children aged 8 to 10 years, for whom it was 35.0%.

Duration of Anaesthetic.—To investigate the effect of duration the figures were divided according to the length of the anaesthetic in minutes (Fig. 2); the vomiting rate rose steadily from 5.4% for the short procedure to 40.8% for anaesthetics lasting six minutes or more.

Type of Operation.—The 3,000 minor operations with which we were concerned could be conveniently divided into five types, and the vomiting rates for these were as follows: removal of toe- or finger-nails, 5.0%; incision of abscess, 6.3%; cauterizing of warts, 20.5%; reduction of fractures or dislocations, 28.6%; miscellaneous procedures—only 40 cases, 32.5%. The vomiting rates for cauterizing warts and the reduction of fractures are four to five times those for the removal of nails and for incisions: these differences are highly significant ($\chi^2>40$, $P<0.0001$).

Interdependence of These Factors

The foregoing analysis, while showing some striking differences in the incidence of vomiting, might have failed to show the individual effects of age, duration of anaesthetic, and the type of operation performed, for these factors were to some extent interdependent. Thus the type of operation influenced the duration of the anaesthetic: it took longer to treat a fracture than to remove a septic nail. The age of the patient tended to determine the type of operation—one-half of all the older patients came up for incisions, but only about a fifth of all children attended for this operation. A further analysis was done to elucidate this matter. We did this by dividing the patients in each operation group into "young" (under 15 years) and "older," and the anaesthetics into "short" (less than three minutes) and "longer." The division was made at 15 years, as this produced the greatest difference between the vomiting rates for "young" and "older" patients, and the choice of durations had a similar effect for "short" and "longer" anaesthetics. The results are given in Table I.

Ten comparisons can be made with regard to duration, and in each case the longer anaesthetics still carried the higher vomiting rate. Similar comparisons between young and older patients show a higher vomiting rate for children for all types of operation, except for the cauterizing of warts taking less than three minutes: here the difference between the vomiting rates for the two age-groups was 1.1%, and this was found not to be significant.

Taking the types of operation performed, the vomiting rates for reductions of fractures and cauterization of warts were again higher than those for removals of nails and for incisions, even after taking into account the ages of the patients and the durations of the anaesthetics.

We have already shown (Fig. 1) that the overall vomiting rate for patients over 50 (12.3%) was higher than for patients between 20 and 50 years of age (7.9%). This difference is significant ($\chi^2=7.0$, $P=0.008$), and is explained by Fig. 3, which indicates that the elderly group contained a disproportionately large number of fracture cases, and we have already shown that such cases carry a relatively high vomiting rate. On comparing the vomiting rates for fracture cases and for non-fracture cases separately in the two age-groups we are considering, the difference in incidence was in each case very small and not significant: old age did not by itself affect the vomiting rate.

The Miscellaneous Operations Group

The high vomiting rate (32.5%) in the 40 patients undergoing miscellaneous operations was probably due to the fact that most of them were accident cases and that 29 of these patients were children (see Table I).

Sex

The incidence of vomiting in the two sexes was next examined. There were 1,510 males in the series, of whom 237 (15.7%) vomited; of the 1,490 females, 203 (13.6%) vomited. This difference is not significant. But in case there could have been confounding with regard to age and the type of operation, we divided the data accordingly, and the results are shown in Table II. It might appear that boys were slightly more prone to vomit than girls, and that women were slightly more

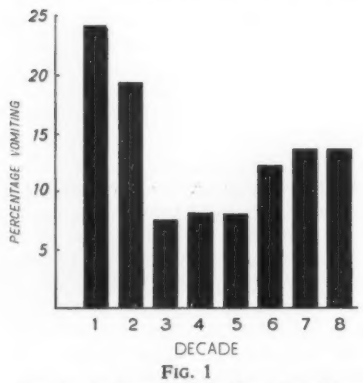

FIG. 1

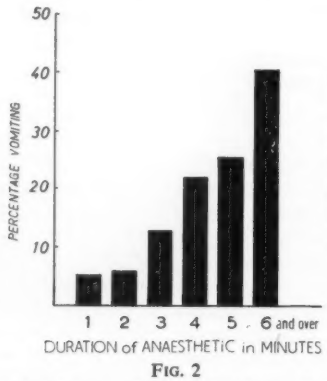

FIG. 2

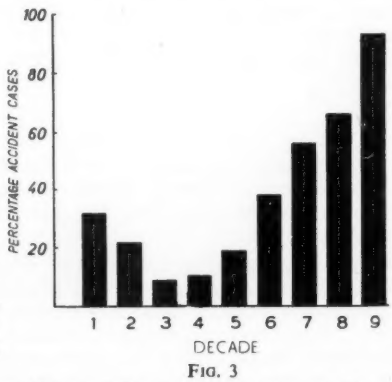

FIG. 3

FIG. 1.—Incidence of vomiting according to patients' ages. FIG. 2.—Incidence of vomiting according to duration of anaesthetic. FIG. 3.—Proportions of accident cases according to patients' ages.

likely to vomit than men; it would, however, require a much larger series to establish such a difference beyond reasonable doubt.

Nature and Quantity of the Vomitus

We have so far studied only the occurrence of vomiting. When we consider the quantity and nature of the material vomited, we find that of the 440 patients who retched or vomited, 326 (74.1%) produced no more than an eggcupful of fluid; 80 (18.2%) produced up to a cupful, generally fluid only; 34 (7.7%) brought up a basinful—large quantities of solid or semi-solid material. Twenty-nine of the patients in this last group had suffered accidents, and received treatment on the same day; they vomited large quantities, in spite of the fact that their anaesthetics had been delayed until at least four hours after the last meal. In 16 of these accident cases the interval from the last meal to the anaesthetic was 4½ hours; in 10 the interval was between 5 and 5½ hours; in two of them it was 6 hours; and in the remaining one the interval was as long as 7½ hours. Of the remaining five patients who vomited copiously but had not suffered accidents on the same day, two were anaesthetized 4½ hours after their last meal; the other three (all teenagers incidentally) afterwards admitted that they had disregarded instructions and had eaten a large meal less than three hours before operation.

Time of Treatment of Accident Cases

In this series 705 patients came with fractures or dislocations: 526 were treated on the same day as their accident and 149 (28.3%) vomited; the 29 who brought up such large quantities were all in this group. The remaining 179 patients with similar injuries attended on the day after the accident, or later, and were given the usual pre-operative instructions with regard to fasting; 53 vomited (29.6%), but on no occasion was the quantity large. Though the incidence of vomiting is almost the same, the difference in those bringing up *very large quantities* in the two groups is highly significant ($P<0.001$).

Discussion

We were here concerned with vomiting as it occurred after the simplest possible anaesthetic. The results were not confused by the effects of other agents or drugs given before, during, or after the procedure. Further, the patient was directly observed by the administrator in every case.

There seems little doubt, so far as short out-patient procedures are concerned, that the age of the patient, the duration of the anaesthetic, and the type of operation done can each directly affect the incidence of vomiting. These factors should therefore be taken into account when designing experiments to assess the effects of drugs or techniques that may influence the vomiting rate.

The age of the patient and the type of operation are not under the anaesthetist's control, but the duration of the anaesthetic can be influenced to some extent, and a good deal of vomiting can be prevented by making the anaesthetic as brief as possible: for instance, the administration need not be started until the surgeon is quite ready. It is doubtful if many of the anaesthetics in our own series could have been made much shorter, but had it been possible to reduce by one minute all those lasting more than two minutes then the total number of patients vomiting would probably have been reduced by over a third.

It is difficult to say what quantity of vomitus is dangerous, but there can be little doubt that the risk is greater for patients capable of producing a basinful of solid or semi-solid material. Fortunately, none of our 34 patients who vomited so much suffered any ill effects, but they present a problem. In this series the time allowed for the stomach to empty was arbitrarily fixed at four hours, and the patients and nursing staff were instructed accordingly. In spite of these precautions, and disregarding those individuals who ignored the instructions, 31 patients vomited so much that it was clear their stomachs had emptied little in four hours. Nearly all these patients were accident cases, having anaesthetics on the same day as their accidents: this

TABLE I.—*Patients Divided According to Operation, Age, and Duration of Anaesthetic*

Age	Duration	Removals of Nails		Incisions		Cauterizations of Warts		Reductions of Fractures and Dislocations		Miscellaneous		Totals	
		No. of Patients	No. Vomiting	No. of Patients	No. Vomiting	No. of Patients	No. Vomiting	No. of Patients	No. Vomiting	No. of Patients	No. Vomiting	No. of Patients	No. Vomiting
Young	Short	59	3 (5·1)	124	8 (6·4)	109	14 (12·8)	56	9 (16·1)	15	1 (6·7)	363	35 (9·6)
	Long	34	5 (14·7)	89	12 (13·5)	234	68 (29·0)	250	114 (45·5)	14	10 (71·4)	621	209 (33·6)
Older	Short	190	5 (2·6)	491	13 (2·6)	72	10 (13·9)	69	6 (8·7)	3	0 (0)	825	34 (4·1)
	Long	115	7 (6·1)	534	45 (8·4)	204	35 (17·1)	330	73 (22·1)	8	2 (25·0)	1,191	162 (13·6)
Totals		398	20 (5·0)	1,238	78 (6·3)	619	127 (20·5)	705	202 (28·6)	40	13 (32·5)	3,000	440 (14·7)

"Young" means under 15 years. "Short" means less than 3 minutes. The numbers in parentheses are percentages.

TABLE II.—*Patients Divided According to Operation, Sex, and Age*

Operations	Males				Females			
	Young		Older		Young		Older	
	No. of Patients	No. Vomiting	No. of Patients	No. Vomiting	No. of Patients	No. Vomiting	No. of Patients	No. Vomiting
Incisions	118	15 (12·7)	513	23 (4·5)	95	5 (5·3)	512	35 (6·8)
Removals of nails	69	7 (10·1)	150	5 (3·3)	24	1 (4·2)	155	7 (4·5)
Cauterizations of warts	174	50 (28·6)	126	23 (18·3)	169	32 (18·9)	150	22 (14·7)
Reductions of fractures and dislocations	186	82 (44·1)	145	24 (16·6)	120	41 (34·2)	254	55 (21·6)
Miscellaneous	23	7 (30·4)	6	1 (16·6)	6	4 (66·6)	5	1 (20·0)
Totals	570	161 (28·2)	940	76 (8·1)	414	83 (20·0)	1,076	120 (11·2)

"Young" means under 15 years. The numbers in parentheses are percentages.

agrees with the often recorded observation that an accident may prolong the emptying time of the stomach. In the light of this experience, it would seem that if a general anaesthetic must be given to a patient who has suffered an accident shortly after eating a large meal the safest course would be to postpone the operation until the next morning and instruct the patient not to have breakfast that day. If this does not prove acceptable to the surgeon then the risk must be faced that in about 1 in 18 accident cases the patient can bring up a dangerous quantity of vomitus four hours or more after the last meal. But, of course, the longer the interval between the meal and the accident the less likely is the stomach to be full.

When by force of circumstance a patient who may not have an empty stomach must be anaesthetized we regard it as sound practice to fill his lungs with oxygen as soon as the nitrous oxide is turned off. This will tide the patient over the brief but dangerous post-operative period when emergence vomiting may occur; if there is breath-holding or momentary obstruction, hypoxia may be avoided.

Summary

Vomiting occurred in 14.7% of 3,000 consecutive out-patients to whom nitrous oxide was administered. Children were more prone to vomit than adults; the longer the anaesthetic the higher the incidence of vomiting; some types of operation carried a much higher vomiting rate than others. The rate was as high as 45.5% or as low as 2.6%, depending on the presence or absence of these factors. Comparative studies are likely to be misleading unless such variability is taken into account.

About 1 in every 18 out-patients undergoing an operation for an injury sustained the same day brought up a potentially dangerous quantity of vomitus, despite an interval of over four hours between the last meal and the anaesthetic.

ACUTE HYPERCALCAEMIA FROM CARCINOMATOSIS WITHOUT BONE METASTASIS

BY

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Hypercalcaemia was for many years linked mainly with hyperparathyroidism, and the effects of the hypercalcaemia *per se* have been overshadowed by the bizarre bone disorder, renal stones, and nephrocalcinosis. In recent years hypercalcaemia has been demonstrated in a number of other disorders and its direct clinical effects have been recognized.

The objects of this case record are to stress the importance of the clinical syndrome of hypercalcaemia and its treatment, and to describe its occurrence with unusual acuteness in carcinomatosis without demonstrable bone secondaries.

Case Report

The patient, a man aged 49, had been perfectly well until six weeks before admission to hospital. For three weeks he was vaguely unwell but able to work; he then became increasingly drowsy, so that he would sleep all day, and, in the last fortnight, complained of abdominal discomfort, constipation, polyuria, polydipsia, and vomiting so severe that he could not keep even fluids down in the previous 48 hours. He had lost 2 stone (12.7 kg.) in this time.

On admission his weight was 14 stone (88.9 kg.), temperature normal, and pulse 90. He appeared pallid but not anaemic. The most striking clinical feature was drowsiness, so marked that he would drop off to sleep while talking. General examination was normal; blood-pressure 150/80.

Investigations on Day of Admission.—Hb, 96%; W.B.C., 7,200/c.mm., normal differential; E.S.R., 6 mm. in 1 hour. Urine: trace of albumin, scanty R.B.C. and W.B.C., no casts, no Bence Jones protein. Fasting blood sugar 95 mg., blood urea 34 mg., serum calcium 16 mg., inorganic phosphate 2.2 mg./100 ml.; alkaline phosphatase 20 K.A. units; serum sodium 138, potassium 2.6, chloride 106 mEq/l.; electrophoresis, slight rise in gamma-globulin; *x*-ray examination showed chest, skull, spine, pelvis, and femur to be normal; electrocardiogram showed features consistent with hypercalcaemia.

A diagnosis of hyperparathyroidism was made and the patient was put on a high fluid intake with glucose and potassium supplements. During the next 10 days vomiting almost ceased and abdominal discomfort subsided. There was no spontaneous bowel action. His drowsiness gradually increased. The serum calcium rose steadily to 18 mg./100 ml., the phosphate remaining below 3 mg./100 ml. The urine output fell and the blood urea rose to 90 mg./100 ml. Urinary calcium excretion was 350 and 550 mg. in 24-hour periods. The hypokalaemia persisted. W.R. was negative.

It was felt to be unsafe to delay any longer, and exploration of his neck was undertaken by Mr. W. H. G. Jessop on the 11th day after admission. A small swelling in the thyroid proved to be a cyst; no other abnormality was found.

He remained unconscious for 36 hours after operation and his condition appeared terminal. The day after operation 100 mg. of hydrocortisone was put in the drip, followed by 100 mg. of cortisone intramuscularly twice daily. Within six hours he began to improve, and next day was able to recognize his relatives, talk, and take fluids. Serum calcium had fallen to 14 mg./100 ml. from a maximum of 18 mg.; blood urea was 77 mg./100 ml. Six days after operation his calcium was 11.5 mg./100 ml., phosphate 3.4 mg./100 ml., and sodium, potassium, and chloride were within normal limits. There was considerable difficulty in maintaining electrolyte balance, particularly in keeping up the serum potassium, and he became increasingly drowsy and the blood urea rose to 158 mg./100 ml. This fell to 105 mg., but the calcium rose again to 16.2 mg./100 ml. in spite of continued cortisone. He died nine days after exploration. Sodium E.D.T.A. had no effect on this terminal rise in calcium.

Necropsy showed widespread abdominal carcinomatosis, the primary being thought to be in the tail of the pancreas, histologically an adenocarcinoma. There was also marked fat necrosis in the omentum, and pancreatitis. Macroscopic examination of several bones failed to show any metastasis.

Discussion

It seems that all this man's symptoms were the direct result of the hypercalcaemia. He never complained of abdominal pain, and such discomfort as he had subsided on admission, when the vomiting also ceased; it seems likely on this history that the pancreatitis found at necropsy was of a few days' duration at most, and unlikely that it caused the hypercalcaemia. The cardinal features of hypercalcaemia are thirst, polyuria, vomiting, lassitude, and loss of weight, mental disorder and drowsiness being particularly marked in acute cases. Other important symptoms are hypotonia, constipation,

and anorexia; calcium deposits or band keratitis may be seen in the eye; isosthenuria, albuminuria, and renal failure are the inevitable outcome, irrespective of the cause.

This clinical syndrome occurs in hyperparathyroidism (Mellgren, 1943; Albright and Reifenstein, 1948). Bradlow and Segel (1956) collected seven cases with acute onset, of which only their patient survived; it was their paper which led us to the exploration of the neck, as delay has been fatal in a potentially curable disease. All these cases had long-standing symptoms of bone or renal disease and may be regarded as "acute on chronic." The syndrome also occurs in myelomatosis (Albright and Reifenstein, 1948), carcinomatosis (Gutman *et al.*, 1936), vitamin D, calciferol, or "A.T. 10" overdosage or sensitivity (Tumulty and Howard, 1942; Danowski *et al.*, 1945), sarcoid (Anderson *et al.*, 1954), the milk-alkali syndrome (Burnett *et al.*, 1949), idiopathic hypercalcaemia of children (Schlesinger *et al.*, 1956), and on immobilization, especially of children, with poliomyelitis (Albright *et al.*, 1941), and fractures (*Ann. intern. Med.*, 1942); it has also been produced by accidental "parathormone" overdosage (Lowenburg and Ginsburg, 1932) and experimentally in animals (Collip, 1925). All these cases show similar features.

In malignant disease, it is thought that bone destruction releases calcium into the circulation. This is only a partial explanation, as the presence of hypercalcaemia does not depend on the extent of the metastases (Gutman *et al.*, 1936; Baker, 1956). Such cases are likely to be seen more often because hormone treatment of carcinoma of the breast may raise the serum calcium (Herrmann *et al.*, 1949; Baker, 1956). Furthermore, cases have now been described in which there is hypercalcaemia when careful post-mortem examination has shown no secondaries in bone (Connor *et al.*, 1956; Plimpton and Gellhorn, 1956). In all these malignant conditions the inorganic phosphate is usually normal or high, but a number of cases have been described in which, as in this case, it was low. Diagnosis may be very difficult, but it seems that the cortisone test is a valuable and rapid means of distinction from hyperparathyroidism, which is the most important differential diagnosis; it has proved ineffective in some cases of carcinomatosis (Plimpton and Gellhorn, 1956). A survey of reported cases suggests that a rapid onset of the syndrome of hypercalcaemia is especially common in malignant disease (Swyer *et al.*, 1950).

The treatment is that of the underlying disease, but Albright and Reifenstein point out that a calcium of 17 mg./100 ml. is the danger point, and, in hyperparathyroidism at least, treatment to prevent death from calcium intoxication before operation is vitally important. In the main, restriction of calcium in the diet and high fluid intake, intravenously if necessary, are all that are required or, indeed, possible. This is an urgent matter and to delay may prove fatal. Symptoms of calcium intoxication can be relieved in most cases of myelomatosis, carcinomatosis (Plimpton and Gellhorn, 1956), sarcoid (Anderson *et al.*, 1954), and hypercalcaemia of children (Creery and McNeill, 1954), by cortisone, and this drug is a valuable form of symptomatic treatment in these circumstances, as well as prolonging life and providing a useful diagnostic test. Sodium citrate and sodium "versenate" (E.D.T.A.) are generally ineffective.

Summary

The clinical course is described of a man aged 49 who presented with features of hypercalcaemia of rapid onset. Necropsy showed carcinomatosis, but there was no sign of bone metastases. The hypercalcaemia was temporarily controlled with cortisone.

I thank Dr. D. Stern for carrying out the necropsy; the resident staff and nurses for their untiring efforts in the care of this patient; and Professor Dent for valuable advice in his management.

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MUCORMYCOTIC GRANULOMA POSSIBLY DUE TO *BASIDIOBOLUS RANARUM*

BY

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This paper is about an unusual case in which biopsy of a subcutaneous mass showed a granuloma containing mycelium of a fungus which, though cultures were not obtained, was thought possibly to be *Basidiobolus ranarum*, one of the rarest causes of mucormycosis. This interpretation was made because of the similar findings by Joe, Eng, Pohan, van der Meulen, and Emmons (1956) in Djakarta in specimens from comparable but more extensive granulomas in two Indonesian children: in one of their cases they isolated a fungus which Emmons identified as *B. ranarum*. The patient whose case is recorded below seems also to have acquired her infection in Indonesia, and this common geographical factor, together with the similarity of the clinical observations and the apparently identical histological findings, is thought to justify the conclusion that the three cases may be of the same nature.

Joe *et al.* (1956) appear to be the only authors who have identified *B. ranarum* with certainty as the cause of human infection. They mentioned two other reports in which infection had been attributed to this organism. One, from the East Indies, concerned a horse (van Overeem, 1925), and the other, from Istria, a gastric

ulcer in a man (Casagrandi, 1931). The case of supposed human infection is very questionable; the infection of the horse took the form of a chronic suppurating granulomatous lesion with a discharging sinus—the lesion was excised and an organism which was thought to be *B. ranarum* was cultivated from it. Joe *et al.* (1956) commented on the pathological dissimilarities between these cases and their own two cases. As *B. ranarum* was isolated abundantly and in pure culture from two successive biopsy specimens in one of their cases there seems to be no doubt about the accuracy of their interpretation of its role as the cause of the lesion. The clinical and pathological similarity between that case and their second case seemed adequate justification for considering the latter to be of the same nature.

B. ranarum is ordinarily a saprophytic mould found in the intestinal contents in frogs and lizards, and in beetles which feed on their dung and which in turn are their prey. It has been identified in various parts of the world, including parts of Europe. It is one of the Phycomycetes, and infection caused by it is therefore considered to be a mucormycosis. In common with the other fungi which cause mucormycoses, *B. ranarum* is characterized by the production in the tissues of a broad infrequently branching mycelium which is without septa. In histological preparations the mycelial filaments often have an appearance reminiscent of lengths of creased ribbon or look like empty and partly collapsed tubules with transparent walls. These appearances, the large diameter of the hyphae, and the characteristic absence of septa enable the mucormycoses to be distinguished readily from other infections caused by myceliate fungi. However, the findings in sections do not enable one to go farther than recognize the presence of a mucormycosis: cultures are essential for the identification of the various species of fungi which cause the infections belonging to this group.

The Phycomycetes—the order to which the fungi which cause the mucorcycoses belong—are widespread in nature as saprophytes, usually on decaying organic matter. Infections by these organisms are infrequent: Hutter (1959) in a review of the world literature was able to find only 116 cases recorded in the hundred years' history of the mucormycoses, and the diagnosis was in doubt in about a fifth of these cases. Pathogenic species of Phycomycetes have so far been recognized in only three families—the Mucoraceae, Mortierellaceae, and Entomophthoraceae. The Mucoraceae are the most important, and include three pathogenic genera—*Absidia, Mucor,* and *Rhizopus*: most cases of deep-seated mucormycotic infection are caused by *Rhizopus oryzae*. The most important clinicopathological form of mucormycosis is cerebral infection, which occurs particularly as a complication of serious metabolic disturbances, especially poorly controlled diabetes mellitus. Cerebral mucormycosis is almost invariably mortal : it has recently been reviewed by Long and Weiss (1959). The only cases of visceral mucormycosis recorded in Britain have been of this type (Kurrein, 1954 ; Symmers and Plummer). There is some evidence that the incidence of at least one of the serious forms of mucormycosis—disseminated haematogenous infection—may be increasing as a result of the increase in the use of certain types of modern drugs (antibiotics and adrenal cortical steroids, and the drugs used in the chemotherapy of malignant diseases) (Zimmerman, 1955).

The case reported illustrates another variety of this rather complex group of fungal infections.

Case Report

The patient, a 13-year-old Dutch girl, was on holiday in London, staying with her grandparents. They went bathing with medical friends, who noticed a thickening of the tissues between her shoulder-blades. The child said that her mother had found this lump about five months earlier, while they were at sea shortly after leaving Indonesia, where she had lived for six years: until then she herself had not known that it was present, for it caused no symptoms. Nothing was done when the lesion was first noticed, and it got progressively smaller. When her English friends noticed it the patient estimated that it had shrunk by about a third.

On examination the lesion had an ill-defined edge but seemed to be about 5 cm. in diameter; it felt as if it was about 1.5 cm. thick at its centre. It could not be moved apart from the skin, which, however, was perfectly normal in appearance. The mass was to some extent movable over the underlying tissues, though there was clearly some fixation to them. The whole mass was uniformly firm in consistency, but not hard; it was only a little tender on firm pressure. The clinical diagnosis was fibroma or lipoma, but as the findings were not typical the possibility of sarcoma was considered and it was thought wise not to take the history of shrinkage of the lesion too seriously into account until the nature of the lesion had been investigated. It was therefore decided to explore the lesion, with a view to its excision.

At operation it proved to be a fibrous and fairly vascular mass, quite tough to cut, and fairly well demarcated from the adjoining subcutaneous tissue though inseparably merged with the overlying dermis. A small wedge was removed from the marginal part of the mass and fixed in formol-saline solution. Paraffin sections were examined on the next day and showed a mucormycotic granuloma (see below). Cultures could not be prepared from the biopsy specimen, and it was not felt justifiable to repeat the operation in order to get further material for cultivation. No discharge occurred from the wound, which healed quickly. No treatment of any sort was given. There was no clinical evidence of any disease elsewhere in the body. *X*-ray examination of the chest and of the nasal sinuses showed no abnormality. Haematological examination was normal and the erythrocyte sedimentation rate was not increased. The patient had no fever.

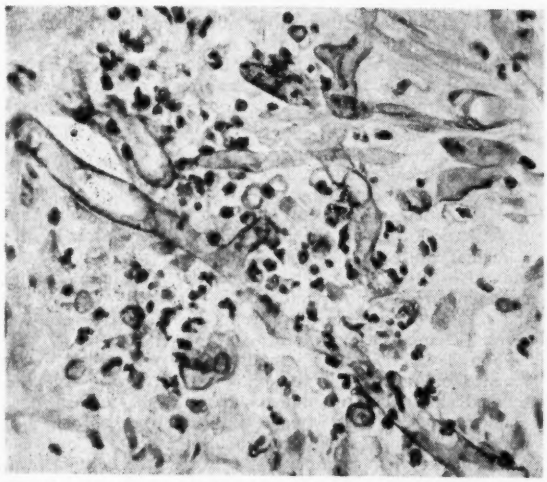
The lesion slowly got smaller and within four months of the operation had disappeared altogether. There has been no recurrence in the period of 18 months which has since passed.

Histological Findings

The biopsy specimen consisted of fibrotic granulomatous tissue containing occasional microabscesses and a scattering of foreign-body giant cells. There was a fairly abundant cellular infiltration, eosinophils being conspicuous in some areas; neutrophil polymorphonuclear leucocytes, lymphocytes, plasma cells, and macrophages were present in various proportions in different areas. The only specific feature about the granuloma was the presence of the hyphae of the fungus: they were not abundant, and only in one field (see accompanying Figure) were several seen together—elsewhere only single hyphae were found among the pus cells in microabscesses, or even occasionally in the cytoplasm of multinucleated giant cells. The hyphae had all the characteristics necessary for the identification of the organism as a member of the order Phycomycetes—their diameter ranged between 7 and 25 microns, they were thin-walled and unpigmented, and they appeared to be completely without septa.

As infection and thrombosis of blood-vessels is a striking feature of the lesions in many cases of the other forms of deep-seated mucormycosis, serial sections of this biopsy

specimen were searched for evidence of vascular involvement: some small thrombosed vessels were found in occasional areas of more active inflammation, but this seemed to be merely part of the inflammatory process in general, and no mycelium was seen in or near any of these vessels. The hyphae were quite readily seen in haematoxylin-eosin preparations, their thin walls being coloured pale blue by Mayer's haemalum: sometimes attention was drawn to their presence by a deposit of eosinophil matter on their surface, and sometimes by the way in which their



Broad non-septate mycelium typical of the fungi which cause mucormycosis: in granulation tissue in the biopsy specimen from the case described. Macrophages, neutrophil polymorphonuclears, and eosinophils are present in the cellular exudate. Periodic-acid/Schiff reaction; Mayer's haemalum. (×375.)

bulk displaced the cellular exudate in the little abscesses. The use of special staining methods added greatly to the ease of demonstrating the organism, particularly when cut across—the periodic-acid/Schiff reaction, Gridley's stain, and particularly Grocott's modification of the Gomori methenamine (hexamine)/silver-nitrate stain gave admirable results.

Comment

This case so closely resembled the two cases recorded by Joe *et al.* (1956) that their identity is scarcely open to question. All three patients were children, the other two being Indonesian boys, aged 4 and 8 years. All of them must have acquired the infection in Indonesia, though its source remains unknown. The lesion was a subcutaneous granuloma in each case, and started on the thorax; there was no history of injury or of any insect bite or the like, which might have been the means by which the organism entered the tissues. The disease was much less extensive in the girl's case than in either of the others: in one of the boys it spread for two years, eventually involving both axillae, both arms, the abdomen, and the buttocks. In all three cases there seems to have been no interference with the general health, and the condition eventually disappeared without any particular treatment being needed. The total duration was about nine months in the cases of the girl and of one of the boys, and over four years in the case of the other boy.

Though *B. ranarum* was isolated in only one of the three cases the evidence seems to justify considering all three to have been of the same nature, particularly in view of the common geographical background and of the virtually identical appearances of the organism and of the tissue reaction in the biopsy specimens from the three cases.

The observation of such a case in Britain is interesting in itself, but this should not obscure the fact that the case described must be regarded as an example of an exotic form of mucormycosis, very different in aetiology and prognosis from the cerebral infection which has been recognized as a naturally occurring, if rare, disease in this country.

Summary

A case of mucormycotic granuloma of the subcutaneous tissue is reported. The patient was a child who had lived in Indonesia until shortly before the lesion appeared. The diagnosis was made histologically. Though cultures were not obtained it is thought that the infection may have been caused by *Basidiobolus ranarum*, as this mould was isolated from one of two virtually identical cases studied in Indonesia by Joe *et al.* (1956).

The lesion disappeared without treatment after a total course of about nine months.

[ADDENDUM.—I am indebted to Dr. Lie Kian Joe, of the University of Indonesia, for information about two further cases of this infection in Indonesian children studied since he and his colleagues reported their first cases (Joe *et al.*, 1956). The clinical picture, pathological findings, and course in the new cases were similar to those originally described.

Dr. Joe and Dr. Chester W. Emmons have kindly allowed me to see sections of the biopsy specimens from their patients. The histological appearances are indistinguishable from those in the case described in this paper.]

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"When the vital statistics of the [fifties] are studied, the remarkable feature is that Aberdeen—never previously in the lead—stepped into first place and retained it. For example: the infant death rate tumbled from an average of 58 per thousand live births for 1940–9 to an average of 24 for 1950–9 (or from 1,790 baby deaths in 1940–9 to 772 in 1950–9), and in the last six years of the decade no Scottish city had in any single year a rate lower than Aberdeen's. The stillbirth rate fell from an average of 24 per thousand total births in 1947–9 to an average of 16 in 1957–9, and in every year of the decade the stillbirth rate was the lowest recorded in any of the cities. The total number of deaths at 1–5 years dropped from 333 in 1940–9 to 120 in 1950–9. The average age at death rose almost year by year from 57.3 in 1947 and 61.7 in 1948 to 67.3 in 1958 and 66.7 in 1959. The tuberculosis death rate per 100,000 population fell from 37 in 1948 and 35 in 1949 to 8 in 1958 and 8 in 1959. Diphtheria (586 cases and 21 deaths in the first year of the previous decade) disappeared—there were 7 cases in ten years, including none in the last four years. Whooping-cough declined from an average of 500 cases in 1950–1 to an average of 76 cases in 1956–9. Ophthalmia neonatorum virtually disappeared. So did scabies and ringworm. Poliomyelitis decreased from 36 cases in 1950 to 10 cases in 1958 and 1 in 1959." (*Health and Welfare*, issued by the Medical Officer of Health, Aberdeen, April, 1960.)

Medical Memoranda

Rupture of the Infarcted Interventricular Septum

Latham (1845) was the first to report rupture of an infarcted interventricular septum (Sager, 1934). In his case "the coronary arteries contained some atheromatous deposits but were quite pervious," and he attributed the pallor and softness of the septum to fatty degeneration.

The first case to be diagnosed before death is that of Brunn (1923), quoted by Sager (1934). Sager reviewed the literature and added a case of his own, bringing the total recorded up to 18. He stated that "acquired perforation of the infarcted interventricular septum is a rare condition which is infrequently diagnosed." Fowler and Failey (1948) again reviewed the literature and added two cases of their own, one diagnosed before death. By that time 54 cases had been reported, 14 of which were diagnosed during life. Edmondson and Hoxie (quoted by Fowler and Failey, 1948), in a review of 25,000 consecutive necropsies performed at the Los Angeles County Hospital over a period of 17 years, found 865 unhealed myocardial infarcts, 72 of which had ruptured and 13 of which had ruptured interventricular septa. Only three of these were diagnosed before death. Arons and O'Rourke (1954) published an unusual case of myocardial infarction in which softening of the interventricular septum resulted in the development of Bernheim's syndrome; this was followed by rupture of the infarcted interventricular septum and the development of complete heart-block within a matter of hours after the perforation, and yet the patient survived for over two months.

Rupture usually occurs within the first two weeks after infarction. It is invariably fatal. Edmondson and Hoxie (quoted by Fowler and Failey, 1948) found the average survival time to be 7.4 days. The longest survival time recorded was four years and ten months (Fowler and Failey, 1948). Weber (1943) attributes the poor prognosis in such cases not to interference with cardiac dynamics but because the perforation is ordinarily seen only in cases of massive infarction. Sager (1934) suggests that the rich anastomotic arterial supply of the septum, as demonstrated by Gross, is the cause of the rarity of this complication. In all the cases he had studied he noticed the narrowing or occlusion of both anterior and posterior descending branches of the left coronary artery. Malone and Parkes (1955) mentioned complete or almost complete infarction of the full thickness of the septal wall as a contributing factor in the development of this complication of myocardial infarction.

The two cases reported below were both diagnosed before death.

CASE 1

A married woman aged 69 was admitted to hospital in November, 1958, as an emergency case after a ? haematemesis. On examination after admission no abnormality was detected in the cardiovascular system. She had no further bleeding after admission, and investigations carried out at the time revealed no abnormality in the gastrointestinal tract, and as she was not anaemic and had no further symptoms while in hospital she was discharged on December 6.

She was readmitted on July 13, 1959, with a history of severe retrosternal pain and vomiting of three days' duration. For six months previously she had had angina of effort. Examination revealed a healthy-looking elderly woman with a regular pulse of 100 and a blood pressure of 140/100, but no evidence of peripheral oedema, no clinical cardiac enlargement, but rather muffled heart sounds. The rest of the examination was negative. The electrocardiogram showed changes of an antero-septal infarction (Fig. 1). The highest level of serum glutamic-oxalacetic transaminase reached on the day of admission was 41 units. She was sedated and started on anticoagulants. She seemed to be making good progress when it was noticed on the morning of July 22 that she was looking rather anxious and orthopnoeic. On examination a harsh systolic thrill was felt over the third, fourth, and fifth left intercostal spaces and a loud, pansystolic murmur was heard over all the precordial area with maximum intensity over the left fourth intercostal space. A diagnosis of ruptured interventricular septum was made. Orthopnoea increased and she became very dyspnoeic on the slightest exertion, as, for example, on sitting up in bed for examination. Evidence of right ventricular failure soon appeared with a high jugular venous pressure, sacral oedema, left parasternal heave, and an enlarged and slightly tender liver. Crepitations appeared at the lung bases. An electrocardiogram taken at the time (Fig. 2) showed evidence of extension of the infarcted area. Treatment with digitalis was ineffective and the patient died four days after the appearance of the murmur.

Necropsy Report.—"Moderate cardiac enlargement, especially of the right auricle and right ventricle. The myocardium of the septum was extremely softened and necrosed and showed a septal defect about 1 cm. in diameter near the base of the heart. The valves of the heart were normal. The coronary arteries showed severe atheromatous changes; the anterior descending branch of the left coronary artery was practically completely occluded. In the liver there were changes of chronic venous congestion, and in the lungs congestion and oedema were present, especially in

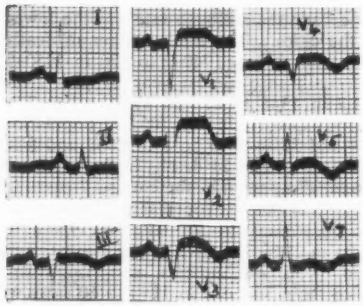

FIG. 1.—Case 1. Electrocardiogram taken on July 13, 1959.

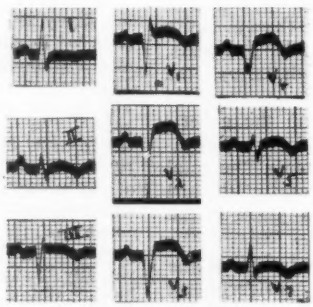

FIG. 2.—Case 1. Electrocardiogram taken on July 22, 1959.

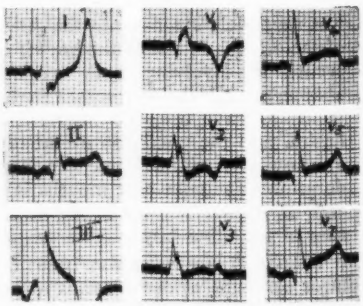

FIG. 3.—Case 2. Electrocardiogram taken on day of admission.

the lower lobes. The bronchi contained a fair amount of mucopus. The remainder of the examination showed nothing of note."

CASE 2

A married woman aged 56, a known case of chronic bronchitis and emphysema, was admitted on September 16, 1959. She had complained of severe retrosternal pain and vomiting for a few days before admission. Examination on admission showed an obese, extremely shocked patient with an imperceptible pulse and unrecordable blood-pressure and blotchy peripheral cyanosis. The apical heart rate, recorded as 40, was regular, with a triple rhythm and a systolic murmur heard over all the precordial areas. No thrill was felt. There were coarse and fine crepitations in the lung bases and the liver was enlarged and palpable 3 in. (7.5 cm.) below the costal margin. A diagnosis of a ruptured septum was made clinically. The haemoglobin was 92%, white blood cells 21,000 (neutrophils 77%, lymphocytes 11%, monocytes 10%, metamyelocytes 2%). The E.S.R. was 4 mm. in the first hour and serum glutamic-oxalacetic transaminase was 300 units. The electrocardiogram (Fig. 3) showed evidence of an extensive posterior and antero-lateral infarction. The patient died two hours after admission.

Necropsy Report.—"The heart was considerably enlarged due to generalized dilatation and to hypertrophy of the left ventricular myocardium. The left coronary artery was slightly atheromatous. The right coronary artery showed advanced atheroma with calcification and evidence of old and recent thrombotic obstruction. There was massive and recent infarction involving the postero-lateral wall of the right ventricle, the posterior part of the interventricular septum, and the adjacent myocardium of the posterior wall of the left ventricle. A linear tear in the posterior part of the interventricular septum was demonstrated. This tear was 4 cm. in length, beginning 4 cm. above the apex of the heart. In its lower 2 cm. the tear extended through the entire thickness of the septum, resulting in a communication between the two ventricles."

COMMENT

Rupture of the interventricular septum may not be as rare a complication of myocardial infarction as originally thought. Growing recognition of this fact has resulted in more cases being diagnosed before death. The perforation is often small and may be easily missed at necropsy. Sager (1934) injected saline into the aorta at necropsy and watched it appear in the right ventricle. This procedure should be carried out in all cases in which this complication is suspected, and the use of a colouring material may facilitate its detection. Though the perforation may be small, the shunt, contrary to what Sager (1934) suggests, is often considerable. This has been proved by catheter studies in some cases and is borne out by the clinical picture in the first case. The pulse in that case had a collapsing quality and there was clinical evidence of right ventricular failure.

The presence of a large left-to-right shunt undoubtedly is a contributing factor in the poor prognosis in such cases, apart from the fact that this complication usually develops after an extensive infarction. This is particularly true of cases in which the perforation occurs late, as in the first case. The left-to-right shunt throws a burden on the myocardium, which is already taxed by the inadequate coronary circulation and the presence of the infarcted muscle. Under such circumstances congestive failure is apt to develop and to progress rapidly. One patient mentioned by Hayward (1955) lived one year with orthopnoea, recurrent acute pulmonary oedema, and severe right-sided failure. Hayward compared such cases to others in which an acquired left-to-right ventricular shunt occurs in patients with healthy myocardium, such as the rupture of a sinus of Valsalva aneurysm into the right heart, and in which the sudden increase in pulmonary flow may not cause oedema of the lung. Among seven cases reported by Malone and Parkes (1955), five showed intense vascular congestion and central zonal necrosis of the liver lobules, and in one case the liver damage was such as to result in jaundice.

One interesting feature in the first case was the appearance of marked exertional dyspnoea with orthopnoea, before any clinical evidence of pulmonary congestion could be detected. The flooding of the pulmonary circulation with blood after the development of the left-to-right shunt in the presence of a failing left ventricle resulted in interstitial oedema of the lungs, giving rise to dyspnoea in the absence of any signs in the lungs. The same phenomenon is noticed in the very early stages of acute pulmonary oedema due to acute left ventricular failure, but it is seldom observed in practice.

The absence of a thrill and the unimpressive murmur in the second case can be explained by the severe peripheral circulatory failure and consequently the low cardiac output, and also the feeble cardiac contraction due to the extensive necrosis. The development of such a murmur in a patient with an acute myocardial infarction who was known previously to have no valvular lesion should always raise the suspicion of the development of a ruptured interventricular septum. Other lesions which may give rise to a similar murmur under such circumstances, and their differential diagnoses, were discussed by Fowler and Failey (1948).

As noticed by Sager (1934), in both these cases there was extensive narrowing or occlusion of the coronary arteries and their branches.

I thank Dr. A. A. M. Nicol for permission to publish this article and for his help and encouragement.

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In the sixteenth century, when the Knights of St. John of Jerusalem arrived in Malta, the population of the island was recorded as being 15,000. The present population is more than 300,000 on an area of 95 square miles, giving a density of nearly 2,700 per square mile, one of the highest in the world. Malta has no artesian wells, and the amount of water extracted from all sources to meet the needs of the population has been steadily growing over the years, reaching an average of more than 277 million gallons a month. In Malta, as in all of Europe, provision of pure water supplies is becoming increasingly difficult as a result of pollution of water resources, and this problem is being studied by the W.H.O. Regional Office for Europe. Several training courses for sanitary engineers have been organized, and measures designed to decrease water pollution have been taken by a number of European countries. (W.H.O. Regional Office for Europe.)

Reviews

PANORAMA OF SCIENCE

A Short History of Scientific Ideas to 1900. By Charles Singer. (Pp. 525+xviii; illustrated. 35s.) Oxford: Clarendon Press: Oxford University Press. 1959.

Nearly twenty years ago Professor Singer's *Short History of Science* was published and welcomed, but it is now out of print. The present volume is based on the former book, but is considerably larger and it "stresses ideas more than formerly" and "pays more attention to simple philosophical implications." The result is excellent, for the careful reading of the text provides a liberal education in the principles of science and in some important aspects of philosophy.

The book begins with the question "What is Science?"; and in his answer the author specially stresses the progressive acquisition of knowledge implicit in scientific work. The arrangement of the chapters exemplifies this progress. Beginning with "The Rise of Mental Coherence" in the early civilizations, we soon get on to the "Great Adventure" experienced in the flourishing period of Athens and "The Second Adventure" at Alexandria. Then come "The Failure of Inspiration" during the time of the Roman Empire, and "The Failure of Knowledge" during the Middle Ages. We are finally introduced to the growth of scientific ideas following "The Revival of Learning" leading up to the more modern "Mechanical World" with its tendency to determinism.

It is a magnificent panorama, but Professor Singer expresses his doubts as to the validity of any mechanical explanation and states his belief that science has its limits. Thus he writes: "Science must keep to the phenomenal level," and, "A mystery does not cease to be mysterious either by limitation in space and time or by re-expression in terms of the unknown." Again he writes: "Ultimate reality cannot be reduced to a conceptual form," and asks, "How do our senses convey anything to us? That, no man can answer."

The reader will regret that the story stops at the beginning of this century, and will look forward hopefully to a future edition in which the recent exciting period may be included.

ZACHARY COPE.

MEGALOBLASTIC ANAEMIAS

The Megaloblastic Anemias. By Victor Herbert, M.D. (Pp. 162+vi; illustrated. $6.) New York and London: Grune and Stratton. 1959.

One of the delights of reading current medical literature is to see new planets or constellations swim into one's ken, and students of pernicious anaemia cannot fail to have noticed the work of Herbert and his colleagues in New York on the mechanism of action of intrinsic factor, the estimation of folic acid in serum, and a number of allied topics. Dr. Herbert's name will now become even better known as a result of this review of the megaloblastic anaemias, which is particularly concerned with their aetiology and classification.

Although a small book which can be read in two or three hours, it contains references to over 600 articles, most of them published within the last five years, and it is of equal interest to the general medical reader and to the research worker. The megaloblastic anaemias are discussed in terms of their incidence, morphology, biochemical basis, aetiological classification, clinical picture, diagnosis, and treatment. Dr. Herbert emphasizes the value of the blood smear in the preliminary diagnosis of pernicious anaemia, because macrocytosis and a shift to the right in the Arneth count are found at an early stage. The simple test is therefore of value in screening groups such as the old and the insane, in whom pernicious anaemia is often missed with unfortunate results. Doubtful smears should be compared with normal smears of peripheral blood and bone-marrow if the earliest changes are to be recognized. The more sophisticated reader will be interested in the suggestion that deficiency of vitamin B_{12} can be produced by long-term ingestion of calcium-chelating agents such as sodium phytate, or that the presence of intrinsic factor in gastric juice can be tested *in vitro*.

One of the key problems in the megaloblastic anaemias is the diagnosis of folic-acid deficiency, and Dr. Herbert has been disappointed in the recently introduced test which depends on the excretion of formiminoglutamic acid in the urine in folic-acid deficiency. He believes that a reliable test for folic-acid levels in the serum is now becoming available; this will enormously simplify the classification of the megaloblastic anaemias. Dr. Herbert is to be congratulated on having brought so much information together in so concise and readable a form.

L. J. WITTS.

PICTURES OF BLOOD VESSELS

Angiocardiopneumographie Élargie. Méthode d'Opacification Vasculaire Générale par Voie Veineuse. By P. Viallet, L. Sendra, L. Chevrot, P. Aubry, and P. Combe. (Pp. 107; illustrated. 4,400 fr.) Paris: Masson et Cie. 1959.

Under the elaborate title of *Extended Angiocardiopneumography* the authors describe their method of producing general vascular opacification by an injection into a peripheral vein of a bolus of contrast material. The key to success lies in correct timing and in making the injection in such a way that the bolus remains as undiluted as possible in its passage through the various parts of the vascular system (arterial and venous); it can thus be followed radiologically in whichever part is being studied.

This book is beautifully produced and well written in French; in it the method is discussed, with its risks and the results obtained. The risks seem to be the same as for other methods of angiography. Very impressive and clear pictures of the heart, the aorta and its branches, the venae cavae and their tributaries, and the pulmonary and hepatic vascular beds are shown, all from a single injection into a peripheral vein; but the contrast has probably been improved photographically in the reproductions. This indirect method is inferior to direct arteriography in the morphological study of the peripheral arteries (carotids, lower aorta, femorals), and on this the authors agree. It does, however, allow a functional assessment to be made. But, on the other hand, in studies of the radiographically more difficult vessels like the great vessels, the pulmonary vascular bed, and the systemic venous return very good pictures can be obtained by this simple method.

All concerned with angiography will want to read this book.

C. G. ROB.
G. H. JANTET.

NUTRITION AND THE PUBLIC

Nutrition and the Public Health. By H. E. Magee, M.B., B.Ch.(Belf.), D.Sc (Aberd.), M.R.C.P. With a foreword by Sir John Charles, K.C.B., M.D., F.R.C.P., D.P.H., Hon.D.Hy. (Pp. 151+xii. 25s.) London: Pitman Medical Publishing Co., Ltd. 1959.

This is a well-written informative little book containing the basic facts about nutrition as viewed from the angle of public health and welfare. Its author played a long and important part in our national food policy, and he still maintains his keen interest in the subject.

Reference to the Wolff Integrating Motor Pneumatograph would have brought the energy section up to date, and reference to the formula for ethyl alcohol could have been omitted. One may cavil that the author uses the slack way of expressing energy value in terms of large calories by spelling "calorie" with a small c instead of writing "Calorie." The simplest and best way is to express energy value in dietary studies as "kilocalories" or "kcal." American colleagues please follow.

The tendency to abridge the text has led the author on occasion into some rather misleading short cuts, such as when on p. 21 he states that the amino-acids (and polypeptides) of the dietary protein on absorption reach the liver and are combined to form the serum proteins.

But these are minor criticisms and do not detract from a most readable account of the physiology of nutrition and of public health interests in what is really the meeting-place of a number of sciences. There are also chapters on growth, malnutrition, public-health methods in nutrition, and diet and disease; also on diets and food habits, food additives, and chemical residues.

D. P. CUTHBERTSON.

DERMATOLOGY FOR SPECIALISTS

General Diagnosis and Therapy of Skin Diseases. An Introduction to Dermatology for Students and Physicians. By Hermann Werner Siemens, M.D. Translated by Kurt Wiener, M.D. (Pp. 324+vii; illustrated. 75s.) Chicago: University of Chicago Press. London: Cambridge University Press. 1958.

This book is essentially for the specialist dermatologist. It is limited to the problems of diagnosis and treatment, indeed almost to diagnosis from the appearance of skin lesions alone and treatment by local measures. From this point of view it is a remarkable production and enters into close detail often in a fascinating manner. The black-and-white illustrations are numerous and excellent, and in themselves constitute a valuable atlas of skin diseases. The work portrays the author with its elaborate classifications and the correlation of morphological detail with terminology and nomenclature. Some eight pages are devoted to anatomy and histopathology, six pages to systemic aspects, and five pages to subjective symptoms and taking a history. There are, however, 15 pages on the colour of lesions, nearly 100 pages devoted to morphological details and to classification on that basis, and a further 22 pages on the extent, shape, and distribution of lesions.

Professor Siemens does not see dermatology as a part of general medicine but as a distinct and separate entity, and the attempt to correlate the skin with the whole is to him a reactionary and retrograde step. The taking of a history, he believes, is relatively unimportant, and general examination other than that of the skin is rarely profitable. Jonathan Hutchinson felt that the development of a specialty should eventually bring it back into closer touch with the whole of medicine, which it would thereby enrich. Professor Siemens's textbook is a fine work within its limitations. It will interest the dermatologist and be invaluable to the dermatologist in training, and even to the general practitioner provided its limitations are recognized. It is not a book for the medical student.

J. T. INGRAM.

SYMPOSIUM ON HAEMOGLOBINS

Abnormal Haemoglobins. A Symposium Organized by the Council for International Organizations of Medical Sciences. Edited by J. H. P. Jonxis and J. F. Delafresnaye. (Pp. 427+ix; illustrated. 45s.) Oxford: Blackwell Scientific Publications. 1959.

This book consists of the text of 26 papers given at a symposium held in Istanbul in September, 1957, in addition to summaries of the discussion following each group of papers and a short section on conclusions and haemoglobin nomenclature. A general bibliography in which at least 600 papers and their titles are given completes the work.

This appears to be the most complete and far-reaching work on the abnormal haemoglobins which has yet been published, and many of those who have contributed most to the astonishing growth of knowledge about human haemoglobin and its genetic variants can be found among the list of participants. The abnormal haemoglobins have a world-wide geographical distribution, and this was reflected in the number of countries—no less than twenty—represented at the symposium.

The papers naturally varied in importance. The first group dealt with general topics such as the heterogeneity of haemoglobin, methods of separation, serological differentiation, foetal haemoglobin, and the clinical and genetic aspects of the haemoglobinopathies and thalassaemia. The second group dealt with the fascinating topic of the geography of the haemoglobins and the factors responsible for their peculiar geographical distribution. Although no doubt some of the papers given contained little that had not been said or published elsewhere, this appears to be by no means true of all.

In a rapidly expanding subject no book can be expected to be up to date when published, the more so when it is a compilation of papers from many parts of the world. The present volume published about 18 months after the symposium is no exception. The reader, nevertheless, is likely to appreciate that he is being given the chance of overhearing a stimulating discussion, which, although perhaps now somewhat dated, at the time represented the last word on the subject.

J. V. DACIE.

STEROIDS

Steroids. By Louis F. Fieser and Mary Fieser. (Pp. 954+xvii; illustrated. £7 4s.) New York: Reinhold Publishing Corporation. London: Chapman and Hall, Ltd. 1959.

This book is a descendant of that first published in 1936 under the title *Natural Products Related to Phenanthrene*, of which the third edition appeared in 1949. The present volume replaces what might have been the fourth edition of its highly revered chemical ancestor; it appears with a shorter title and is an even more striking example of a concise text which is at once comprehensive and readable. Many investigators sent copies of papers in press to the authors, so that much

literature up to the spring of 1959 has been included. Although the book is naturally largely chemical, and of greatest interest to chemists and biochemists, brief summaries of the biological properties of physiologically active substances are included which will help to relate chemical properties to biological activities. The biosynthesis of many of the steroids is also discussed and consideration of their katabolism in the animal body included. The authors claim that their book is written from the perspective of modern theory. That such an aim is consonant with a concise and clear text is amply demonstrated.

F. G. YOUNG.

TUBERCULOSIS IN MALAYA

Treatment of Lung Cavities and Endobronchial Tuberculosis. With Special Reference to Treatment in Malaya. By Beryl E. Barsby, M.D., M.R.C.P. (Pp. 147+vi; illustrated. 20s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1959.

Endobronchitis may influence greatly the progress and manifestations of pulmonary tuberculosis. Its importance in clinical management has perhaps declined with the introduction of powerful anti-tuberculous drugs and the lessening use of surgical and collapse therapy, but knowledge of the possible effects of endobronchitis remains an essential to the doctor who tries to treat tuberculosis intelligently. To such this book will be of interest. Dr. Barsby has carried out careful bronchoscopic and bronchographic studies on her patients and presents here the fruits of her experience. Some of the views she expresses will not meet with general acceptance. She advocates cortisone in the management of certain patients with organisms resistant to the standard anti-tuberculous drugs. There is much published evidence to indicate the dangers of such a procedure, and the author does not produce enough evidence to justify any change from accepted practice. In a discussion of collapse therapy she states that under Oriental conditions it is still " very useful, but on no account should it be used in an attempt to close a cavity." Accumulating experience with chemotherapeutic drugs, and better knowledge of their use, makes it doubtful if collapse therapy produces any significant advantage after a cavity has closed.

The work which forms the background for this study was carried out mainly in Malaya, and not the least interesting aspect of the book is the insight it gives of some of the peculiar problems which may confront the doctor practising in less developed regions. There are useful chapters in the book dealing with anaesthesia for bronchoscopy, the management of tuberculous pyopneumothorax, and aspects of thoracic surgery, including physiotherapy.

J. D. ROSS.

Surgical Progress, 1958, is the eighth of an annual series of supplements to *British Surgical Practice*, under the general editorship of Sir Ernest Rock Carling and Sir James Paterson Ross. The material may as usual be classified under the three familiar headings: subjects which have not been dealt with before—the collagen diseases, operative cholangiography, the carpal-tunnel syndrome, the use of the ileum in urology, and pre-clinical carcinoma of the cervix; subjects which have been brought up to date; and critical surveys of recent work—in the surgery of the stomach and duodenum, in pulmonary surgery, and in the surgery of the central nervous system. These surveys are followed by abstracts relating to the subject. There is also the traditional noter-up section. (Butterworth and Co. (Publishers) Ltd.; 44+ix pp., 98 figs., index, 52s. 6d.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Proceedings of the First National Biophysics Conference, Columbus, Ohio, March 4-6, 1957. Edited by Henry Quastler and Harold J. Morowitz. (Pp. 756+xxvii; illustrated. £6.) New Haven: Yale University Press. London: Oxford University Press. 1959.

Die Männliche Keimdrüse: Struktur - Funktion - Klinik. Grundzüge der Andrologie. By Professor Dr. E. Tonutti, Dr. O. Weller, Professor Dr. E. Schuchardt, and Professor Dr. E. Heinke. (Pp. 272+xii; illustrated. DM. 79.) Stuttgart: Georg Thieme Verlag. 1960.

Delinquency and Parental Pathology. A Study in Forensic and Clinical Psychology. By Robert G. Andry, M.A., Ph.D. (Pp. 173+xv. 21s.) London: Methuen and Co., Ltd. 1960.

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MASKS OR SILENCE

When a healthy person remains silent, no organisms come from his mouth or nose, but when he speaks, coughs, or sneezes large numbers of the commensal organisms usually present in the nasopharynx, such as *Streptococcus salivarius, Streptococcus viridans,* and *Neisseria catarrhalis,* are expelled into the air. The assumption was therefore made many years ago that, if pathogenic organisms such as *Streptococcus pyogenes* and *Staphylococcus aureus* are also present in the nasopharynx, they, too, will be expelled in sufficient numbers to justify the wearing of masks as part of the ritual of an operating-theatre or delivery room. Nevertheless, it has not, in fact, been shown that these two pathogens are expelled in large numbers. In the particular case of *Str. pyogenes* it was first found by A. L. Bloomfield and A. R. Felty[1] in 1924, and since then by other workers,[2 3] that both carriers and patients with tonsillitis or scarlet fever expelled so few when talking, coughing, or sneezing that culture plates held in front of the mouth were more often than not found to be free of this organism.

Even when a carrier puts himself into the same position as a surgeon while performing an operation, and talks in a fairly loud voice for five minutes directly downwards on to a culture plate 12 inches (30 cm.) away, he may fail to project this organism on to it. In one series of experiments only 3 out of 12 carriers were able to do so, and even when this organism did appear on the culture plates not more than one or two colonies were obtained.[4] The probable reasons for the infrequency with which this streptococcus leaves the mouth would seem to be that it can be expelled only in droplets, that these droplets consist of saliva derived almost exclusively from the front of the mouth,[5] and that, for some as yet unknown reason, the saliva in this part of the mouth contains few *Str. pyogenes,* even when the individual is in the throes of an active infection such as tonsillitis or scarlet fever.[6]

Staph. aureus is found so infrequently in the mouth that its expulsion in droplets of saliva is improbable. It parasitizes a small area of skin in the front of the nose. The air passing over this area when the person remains silent does not pick it up, for it does not appear on culture plates held directly beneath the nostrils. If, therefore, it emerges it is more likely to do so in droplets, but it is improbable that droplets are in fact expelled in any numbers. Examination of flashlight photographs during activities such as talking and coughing which bring about the expulsion of large numbers of droplets from the mouth show clearly that comparable numbers of droplets are not expelled from the nose. Indeed, even when sneezing virtually none emerge from the nasal orifices.[7 8] It need cause no surprise, therefore, that when culture plates are held beneath the nose while talking, coughing, or sneezing they collect very few organisms of any kind, and even if the subject is a nasal carrier of *Staph. aureus* this organism is generally conspicuous by its absence.[9]

Confirmation of this has recently come from the work of R. A. Shooter, M. A. Smith, and C. J. W. Hunter,[10] who, in experiments with 129 normal subjects, ascertained the number of organisms emitted into the environment while the subjects were silent or conversing in the fairly low tones usually employed in an operating-theatre. For this purpose the individual sat with the head protruding through a hole in a table, on the surface of which were disposed 20 culture plates at varying distances from the mouth, with some at the side of, and behind, the head. The whole table, including the head of the subject, was enclosed in a plastic cover to exclude draughts. When 21 known carriers of *Staph. aureus* talked for 15 minutes in this apparatus, only three colonies of this organism were obtained on the 420 culture plates which were exposed. Since this involves a total period of five and three-quarter hours of steady conversation, it can only be concluded that in order to make certain he will project one droplet containing *Staph. aureus* on to one or other of the culture plates a carrier must, on the average, talk continuously for nearly two hours. Thus the possibility that a carrier of *Str. pyogenes* or *Staph. aureus* who is talking can project his own organisms into a wound while bending over it would seem to be remote but not completely impossible. Use of a mask when conversation is imperative is therefore a sensible precaution. But is it necessary to devote

[1] Bloomfield, A. L., and Felty, A. R., *Johns Hopk. Hosp. Bull.*, 1924, **35**, 115.
[2] Colebrook, L., *Brit. med. J.*, 1933, **2**, 723.
[3] Paine, C. G., ibid., 1935, **1**, 243.
[4] Hare, R., *Canad publ. Hlth J.*, 1940, **31**, 539.
[5] Duguid, J. P., *Edinb. med. J.*, 1945, **52**, 385.
[6] —— *Brit. med. J.*, 1946, **1**, 265.
[7] Jennison, M. W., *Sci. Mon. (Lond.)*, 1941, **52**, 24.
[8] Weyrauch, F., and Rzymkowski, J., *Z. Hyg. Infekt.-Kr.*, 1938, **120**, 444.
[9] Hare, R., and Thomas, C. G. A., *Brit. med. J.*, 1956, **2**, 840.
[10] Shooter, R. A., Smith, M. A., and Hunter, C. J. W., *Brit. J. Surg.*, 1959, **47**, 246.

time, trouble, and expense to devising elaborate and unusually impervious masks to catch the odd infected droplet that very occasionally emerges ?

The further work of Shooter and his colleagues provides an answer to this question. Using the apparatus already mentioned, they experimented with three types of mask. One consisted of four layers of gauze, a second of two layers of cambric with a paper deflector in front of the mouth, and the third was a disposable paper mask. The total number of organisms of all kinds appearing on the plates, exposed when normal persons conversed while wearing them, was, as might have been expected, lower than when they conversed without them, but the number of organisms obtained was almost exactly the same whatever type of mask was worn. The only difference in their performance—and even this was slight—was that the mask with the paper shield deflected organisms on to plates at the sides of the head to a greater extent than did the other masks. It is also noteworthy that the counts obtained were about the same as those obtained when unmasked subjects remained silent. The only conclusion it is possible to reach is that so few droplets carry pathogenic organisms that almost anything placed in front of the mouth will suffice to catch them, and if it is possible to impose a complete ban on conversation nothing at all need be worn.

There is indeed much to be said for the second alternative, because a mask that has been worn for some time can become very dangerous, for it comes into close contact with the nose and upper lip, both areas that are heavily contaminated by *Staph. aureus* when the wearer is a carrier. It can, accordingly, become contaminated in turn. Examination by Shooter and his colleagues of 53 masks after use for some time in the theatre by nasal carriers of this organism showed that no fewer than 33 were contaminated on the inside and 21 on the outside. If, then, such a mask is handled in any way, or, as is not unusual, put into the pocket, both the fingers and the clothing of the carrier will become more heavily contaminated by his own organisms than they would have been if he had not been provided with a mask.

MALABSORPTION SYNDROME

The small intestine is the crucial part of the digestive system. Within its lumen most of the processes of digestion take place and it is also responsible for absorbing the products of digestion, although water and electrolytes are also absorbed from the large intestine. During recent years it has become conventional to include within the term malabsorption syndrome a variety of clinical symptoms and signs which may occur when either digestion or absorption is impeded. It is not a precise diagnosis. Indeed, as soon as a patient is recognized as suffering from the malabsorption syndrome it is the duty of the clinician to try to make an exact diagnosis of the underlying cause, so that correct treatment can be given. The small intestine is a relatively inaccessible organ for clinical study, but many techniques have been developed in recent years which have increased our understanding of its physiology and pathology, and are rapidly becoming essential investigations in everyday clinical medicine. Most of these techniques have recently been discussed in an excellent symposium.[1]

The underlying processes involved in the malabsorption syndrome are of two main types. On the one hand, digestion may be defective ; on the other, malabsorption may be the essential disturbance. Among the conditions which result in maldigestion, diseases of the pancreas and of the biliary system are prominent. In chronic pancreatitis and in cystic fibrosis of the pancreas (mucoviscidosis) the external secretions of the pancreas are so limited that inadequate digestion occurs. The result is that fat is poorly digested, with resulting pancreatic steatorrhoea, and proteins are likewise poorly digested, with heavy loss of nitrogen in the faeces. Carbohydrate metabolism on the other hand, is well maintained, because simple sugars are readily absorbed. Likewise, anaemia is not a common symptom because iron salts, folic acid, and vitamin B_{12} are also usually well absorbed. Since the defect is essentially due to lack of pancreatic digestive enzymes some benefit may be obtained by giving pancreatin with meals, although its use is usually disappointing.

Any patient with obstructive jaundice suffers from inadequate digestion of food, especially of fats, with resulting steatorrhoea, and this is the main cause of the pale stools of obstructive jaundice. When the obstructive jaundice is brief the steatorrhoea is overshadowed by other symptoms and it does not persist long enough to cause serious harm. With chronic obstructive jaundice serious effects arise from the steatorrhoea, especially bony changes in the form of osteomalacia and osteoporosis.[2] Attempts have been

[1] *Brit. J. Radiol.*, 1960, **33**, 201.
[2] Atkinson, M., Nordin, B. E. C., and Sherlock, S., *Quart. J. Med.*, 1956, **25**, 299.
[3] Lundh, G., *Acta chir. scand., Suppl.*, 231, 1958.
[4] Butler, T. J., *Gut*, 1960, **1**, 55.
[5] Jackson, W. P. U., in *Modern Trends in Gastroenterology*, 2nd series, edited by F. Avery Jones, 1958, London, p. 243.
[6] Meyer, H. W., *Ann. Surg.*, 1954, **140**, 447.
[7] Sheldon, W., and Lawson, D., *Lancet*, 1952, **2**, 902.
[8] French, J. M., Hawkins, C. F., and Smith, N., *Quart. J. Med.*, 1957, **26**, 481.
[9] Shiner, M., *Gut*, 1960, **1**, 48.
[10] Doniach, I., and Shiner, M., *Brit. J. Radiol.*, 1960, **33**, 238.

made to overcome the digestive disability in obstructive jaundice by giving bile salts by mouth, but without success.

Disordered digestion within the small intestine can also arise when the secretions of the pancreas and biliary system are both normal. In the rare Zollinger–Ellison syndrome there is a remarkably heavy and continuous secretion of gastric juice which is a consequence of the presence of non-insulin-secreting tumours of the pancreas. The usual manifestation of the condition is severe peptic ulceration of the stomach and duodenum, often atypical in distribution and behaviour. Some patients, however, escape peptic ulceration and have diarrhoea with steatorrhoea, and the most likely explanation for this appears to be that the quantities of highly acid gastric juice secreted are so large that the contents of the small intestine are rendered acid instead of being slightly alkaline, and consequently the pancreatic enzymes are unable to function. Maldigestion also occurs after major operations on the stomach. Total gastrectomy almost invariably produces a gross disorder of digestion, while it is not very rare for partial gastrectomy to do likewise. From the studies of G. Lundh[3] it appears that a major factor in this type of disturbance is that the food enters the small intestine so quickly that it travels down before the pancreatic juice and bile can be secreted and become intimately mixed with it. The amounts of pancreatic enzymes secreted are also reduced.[4]

Disordered absorption can occur in a variety of ways. The simplest case is when there is actual loss of a large part of the small intestine—for example, when it has been necessary to carry out extensive surgical resection because of a gunshot wound in the abdomen. Some degree of dysfunction then occurs, because there may be inadequate opportunity for fats and proteins to be both digested and absorbed during the time that the food is travelling through the shortened intestine. But remarkable examples are on record of patients surviving for many years with only a very small length of small intestine.[5,6]

Organic diseases of the small intestine are also prone to disrupt its function. Elsewhere in this issue (p. 1324) Drs. Margaret J. King and R. A. Joske report what they believed to be a temporary phase of malabsorption in two patients who had had severe acute enteritis. Any order which leads to a stricture in the small intestine may cause malabsorption, and this is probably the causative mechanism in untreated Crohn's disease. Tumours of the small intestine are uncommon, but when they do arise they may present as the malabsorption syndrome through causing a stricture of the intestine, although some lymphosarcomata are multiple and so extensive that the actual absorbing surface may be effectively reduced. Whenever a blind loop of intestine exists there is the possibility of malabsorption. Such blind loops may occur because of a fistula between one loop of intestine and another or as a deliberate act on the part of the surgeon when he bypasses a portion of diseased intestine, as, for example, when doing a short-circuit operation for Crohn's disease. Thus the malabsorption syndrome may develop in three separate ways in Crohn's disease —because the disease often presents as a stricture, because it may form a fistulous connexion between the diseased segment and another segment of gut, or because of a particular type of surgical operation.

In these examples of malabsorption due to stricture or blind loop it is thought that an important factor in the disturbed absorption is the presence of large numbers of coliform bacteria in the blind loop or above the site of stricture, whereas the healthy small intestine is virtually sterile. The exact processes by which coliform bacilli impede small-intestinal function nevertheless remain uncertain. In any event, a similar mechanism appears to be responsible for the severe malabsorptive state which occurs in gastro-colic fistula, a condition which is usually a complication of recurrent peptic ulceration at or close to the stoma after gastro-enterostomy or partial gastrectomy ("stomal" or "anastomotic" ulcer). The disability is not caused by leakage of food from the stomach directly into the colon, because the communication is usually small and any such loss of food would be readily counterbalanced by eating a little more. The true explanation is that some colonic contents enter the stomach, so that the small intestine swarms with coliform organisms. This view is supported by the finding that rapid improvement is brought about either by oral administration of a broad-spectrum antibiotic or by colostomy proximal to the gastro-colic communication, so that the faecal stream is diverted away from the entry hole to the stomach. The definitive treatment is of course to operate directly on the fistula after due preparation. In the opening pages of this issue Professor A. W. Kay discusses in some detail examples of the malabsorption syndrome of special interest to surgeons.

In coeliac disease and idiopathic steatorrhoea of adults (which are probably one and the same disease) there is a profound disturbance of absorption from the small intestine which affects every class of substance, so that fats, proteins, carbohydrates, vitamins, electrolytes, and even water are poorly

absorbed. In some of these patients the intestinal symptoms, such as diarrhoea with bulky, pale, frothy stools, attract medical attention, but some patients have few or no symptoms directly referable to the gastro-intestinal tract and present with such signs of malabsorption as anaemia (which may be either of the iron-deficiency type or megaloblastic), bony changes (rickets in children or osteomalacia and osteoporosis in adults), tetany, neurological changes, or vitamin deficiencies. In recent years it has been found that these patients respond well to a gluten-free diet,[7 8] though it is uncertain whether the unfavourable action of gluten is closely connected with the essential lesion in the disease, since the histological changes in the small-intestinal mucosa remain unchanged after the patient has responded well to dietary treatment.[9 10]

VIRUSES IN ECLIPSE

Most bacteria, the rickettsiae, and the psittacosis group of organisms are sensitive to one antibiotic or another, whereas the pox group of viruses, and all groups of smaller viruses, are not. This sensitivity is correlated with the larger size of the sensitive organisms, and probably with the possession of some biochemical mechanism different from that of the host. This in turn is a reflection of the fact that the typical viruses multiply in the body in a way fundamentally different from that of the antibiotic-sensitive organisms. Bacteria divide by binary fission, but viruses such as influenza virus and poliovirus reproduce within the cells of the host by a much more complicated and less well understood mechanism. To find some form of therapy for infections such as influenza and poliomyelitis is one of the most pressing problems of medical microbiology.

Virus research in the last ten years has concentrated increasingly on what is happening during replication (i.e., reproduction) of virus within infected cells. This is logical, because it is this process which damages the cells and causes disease. It has been known for some years that the virus particle of the much-studied T bacteriophages, on entering a cell, ceases to exist as an infective entity, and indeed as a physical one even. Evidence now suggests that this is true of some animal viruses also, and in fact Burnet has suggested that the possession of such a phase in the life cycle, the eclipse phase, is a *sine qua non* of true viruses. Until recently knowledge about this phase was as much in eclipse as the virus. It is now known that in some viruses containing ribonucleic acid—for example, poliovirus—the nucleic acid alone can infect a cell,[11 12] and it is the nucleic acid which transmits the genetic identity of the virus to its progeny. This makes the eclipse phase easier to understand, for it is probable that the virus continues to "exist" during it as nucleic acid. Whatever else goes on at this time, there must be the synthesis of more nucleic acid and protein molecules, and the assembly of these within the cell (or, in the case of the influenza group, probably at the surface of the cell[13 14]) to make new particles.

One of the difficulties about studying the eclipse phase with animal viruses has been to be sure that there is such a phase. Being a negative attribute of the growth cycle, it is harder to detect than a positive one, for it must be shown that there is virtually no infective virus present for a period in infected cells. With western equine encephalitis virus in chick cells,[15] and with herpes simplex virus in human carcinoma cells,[16] it has been shown that very little virus can be recovered from infected cells soon after infection with these viruses. The amount is so small that it could not possibly account for more than a tiny fraction of the yield of the progeny if this were produced by binary fission of the particles originally present.

However, even this small amount of residual virus has presented the problem that it is difficult to study the actual period of the eclipse phase so exactly as some would like, and has not easily convinced all critics. K. Yoshino and colleagues[17] have reported experiments on herpes virus growing in the cells of the chorio-allantoic membrane of ingeniously manipulated eggs. Residual virus left outside the cells but not causing infection has been inactivated by ultra-violet irradiation rather than removed by the traditional method of repeated washing and application of anti-serum. These workers claim that the irradiation does not appreciably affect the capacity of the cells to produce virus, and they have shown that, when the cells are infected with herpes virus, no infective virus at all can be recovered for a period of about ten hours. They consider that during this time all the particles taken up by the cell have changed into some form which, while capable of causing the cell to produce progeny virus, is incapable of infecting other cells. Probably, by analogy with the T bacteriophages, it is for at least part of the time in the form of "naked" nucleic acid within the cell.

If the existence of an eclipse phase in even a small number of viruses can be established with certainty, then it is likely that it is a general property of the multiplication of animal viruses. This, more than any other property, widens the already considerable gulf between them and the bacteria. It also makes it clear that to inhibit the growth of viruses within the cells of the body, and hence arrest the progress of acute virus infections, entirely new methods of approach are necessary, such as the experiments with interferon by A. Isaacs.[18]

[11] Colter, J. S., Bird, H. H., Moyer, A. W., and Brown, R. A., *Virology*, 1957, **4**, 522.
[12] Alexander, H. E., Koch, G., Morgan Mountain, I., and Van Damme, O. *J. exp. Med.*, 1958, **108**, 493.
[13] Breitenfeld, P. M., and Schäfer, W., *Virology*, 1957, **4**, 328.
[14] Morgan, C., Rose, H. M., and Moore, D. H., *J. exp. Med.*, 1956, **104**, 171.
[15] Rubin, H., Baluda, M., and Hotchin, J. E., ibid., 1955, **101**, 205.
[16] Stoker, M. G. P., and Ross, R. W., *J. gen. Microbiol.*, 1958, **19**, 250.
[17] Yoshino, K., Taniguchi, H., and Taniguchi, S., *Virology*, 1960, **10**, 97.
[18] Isaacs, A., ibid., 1960, **10**, 144.

EPIDEMIC VERTIGO

Epidemic vertigo is a condition characterized by the sudden onset of severe vertigo and vomiting. The patient is often completely prostrated for several days, being compelled to lie quite still in bed, as any movement of the head gives rise to a recurrence of vertigo. E. Pedersen[1] has recently reviewed the literature on the disease and reported on some epidemics of it in Denmark. The names of epidemic neurolabyrinthitis, vestibular neuronitis, and acute labyrinthitis have often been given to this clinical syndrome, but epidemic vertigo is to be preferred as a title, since although the condition has been recognized for many years its aetiology remains unknown, and even the site of the pathological change responsible for the patient's symptoms has not been firmly established. Even the name epidemic vertigo is not entirely satisfactory, as many such cases are sporadic.

It is impossible to say whether all illnesses of this type are of similar cause, and the differential diagnosis is sometimes a matter of considerable difficulty, since patients with many other conditions, including disseminated sclerosis and infarction in the brain stem, may occasionally present with vertigo. However, in these diseases there are generally other neurological signs which reveal the nature of the underlying lesion. Diagnosis from Ménière's syndrome is not usually difficult, because in this condition the vertigo is generally recurrent and occurs in attacks of comparatively brief duration, while unilateral tinnitus and progressive deafness are usual. It is of course true that in epidemic vertigo, even when the initial symptoms subside, normally after a few days, recurrent vertiginous episodes of diminishing severity, combined with an unsteadiness of gait, may last for several weeks or even for months, and are often associated with persistent lassitude and depression. In general, however, as Pedersen's analysis of over 400 cases occurring in Denmark has shown, the condition is benign and the patient eventually recovers completely. The cases occurred in a total of 25 epidemics, and almost twice as many women as men were affected. Gastrointestinal symptoms (diarrhoea in addition to vomiting) were common in one group of cases, while fever with signs and symptoms of an upper respiratory infection were frequent in a second group. The only definite neurological sign, apart from unsteadiness, was horizontal nystagmus, and this was relatively uncommon. In a single family which included several affected individuals a child developed a severe encephalitis during the epidemic; the diagnosis was confirmed by brain biopsy. Slight loss of hearing was noted in two cases only, but in 7 of 16 patients subjected to lumbar puncture there was a slight pleocytosis of up to 10 mononuclear cells per c.mm. in the cerebrospinal fluid at the height of the illness.

Like many workers before him, Pedersen was unable to determine with certainty the site of the lesion responsible for the illness, and little help was forthcoming from special investigations. He suggests that probably the second vestibular neurone is primarily involved, possibly in the brain stem. A virus infection seems to be the most probable cause, but no organism has ever been isolated. No specific treatment has been discovered, but symptoms may be mitigated by giving antihistamine drugs and their analogues. Some treatment of depression is often needed for a few weeks after the acute stage. Fortunately, when the diagnosis is clear, eventual total recovery can be confidently predicted.

[1] Pedersen, E., *Brain*, 1959, **82**, 566.

CENTRAL CYANOSIS

Cyanosis is commonly classified as central, peripheral, or chemical. The last is usually due to absorption of drugs taken by mouth or of the products of abnormal colonic metabolism; it is detected by the spectroscope, and measurements of arterial oxygen saturation will be normal.

Central cyanosis occurs when blood leaves the left ventricle bearing less oxygen than normal. There must always be some undersaturation of 1–2% because of the bronchial circulation. Undersaturation greater than this will be found when there is a right-to-left intracardiac shunt, a pulmonary arterio-venous aneurysm, or when blood is bypassing inadequately ventilated alveoli. Probably not enough use has been made of measurements of arterial oxygen saturation in assessing the severity of respiratory disease. If done properly, arterial puncture causes no danger or inconvenience to the patient. However, since opinion still inclines against the manœuvre, and suitable laboratory facilities are lacking sometimes, it remains customary to guess the degree of cyanosis by looking at the patient. Central cyanosis is said to be present if it is noticeable in warm parts such as the tongue, and it might be added that doctors will agree it is present only if the oxygen saturation is below 75%.

Is such clinical inspection ever a reliable guide in distinguishing between central cyanosis and the peripheral cyanosis of stagnation? J. H. Comroe and S. Batelho[1] have expressed their doubts about the reliability of cyanosis as a sign, and W. E. Medd and his colleagues[2] have gone into the problem again. The latter set out to assess the reliability of cycanosis of various parts of the body as a guide to arterial oxygen desaturation in patients under ordinary ward conditions. They disagree that cyanosis of a warm part indicates central cyanosis. Cyanosis depends upon the amount of reduced haemoglobin in sub-papillary venous plexuses. When the velocity of blood flow is low, the proportion of reduced haemoglobin will rise, and when there is a sufficient pool of blood in the venous plexus cyanosis will appear. Usually when the flow of blood is high the part is warm and pink, the metabolism is active, the surrounding temperature is high, and the rate of evaporation from the surface is low. Even so it is possible under these circumstances to have a sufficiently sluggish venous pool to produce cyanosis, and Medd and colleagues cite the "port-wine" mark as an extreme example of this. Thus, once again, the point

[1] Comroe, J. H., Jr., and Batelho, S., *Amer. J. med. Sci.*, 1947, **214**, 1.
[2] Medd, W. E., French, E. B., and Wyllie, V. M., *Thorax*, 1959, **14**, 247.

has been made that, while the tongue is probably the most sensitive site for the observation of central cyanosis, intelligent guessing does not replace thorough estimations of arterial oxygen saturation or oximetry.

CANCER IN FIBROTIC LUNG

The difficulty of diagnosing pulmonary shadows in the radiographs of coal-miners has recently been emphasized by R. Abbey Smith.[1] He notes in particular the single fibrotic nodule unaccompanied by radiographic evidence of simple pneumoconiosis and "the slowness in growth of certain lung cancers in miners." In a review of 320 cases operated on for lung cancer at one hospital, and drawn from the general population of town and country, he records that 36% survived two years or more after operation. This figure compares with 34% reported by A. B. Taylor and J. M. Levi[2] in 1954 in relation to 512 resections, and with 42% by J. R. Bignall and A. J. Moon[3] in 1955 in relation to 205. It appears that the "industrial" group of workers fared better than the "agricultural and rural," evidently because of the inclusion in the former of a number of coal-miners, coal-miner being defined as a person "who has worked five years or more underground at the coal face" (no account of geographical situation of the mines was taken). "During the same period with the same criteria of operability," he found that of 21 miners who had undergone resection only three died in the first two years after, which is a survival rate of 86%—a statistically significant difference from the whole.

He offers two possible explanations: first that the coal-miner develops a slowly-growing tumour specific to him; and secondly—which he finds the more probable—that growth of tumour is "retarded by the effects of prolonged inhalation of coal dust on the lung parenchyma and lymphatics." Against the first he quotes W. R. L. James[4] as finding no difference in the frequency of different histological types of carcinoma between miners and non-miners. But it may be that the histological type is not important in this respect, that in fact there may be some factor which operates in coal-miners to slow down the rate of growth of all tumours. If this is so, the factor which improves their prognosis could be akin to that which explains why patients with longer duration of symptoms pre-operatively fare better than those with a short history.[3,5] But Abbey Smith favours the second explanation, the blocking, referred to by F. G. Kergin,[6] of the lymphatics by carbon-laden macrophages and the choking of the glands by heavy carbon deposits and fibrosis, making lymphatic metastasis difficult. Kergin has drawn attention also to the fibrous tissue binding glands to blood vessels and bronchi, so often found in the lungs of coal-miners. It may be that lymphatic[7] as well as vascular[8] invasion and metastasis are hindered, though James found no difference in the incidence of metastasis to different organs in the miner and non-miner except for the brain, in which secondary deposits were found in only 9% of miners and 27% of non-miners.

This paper shows that experience is better distilled to statistics than to *obiter dicta*. It is a reminder of the theory that previous damage may mitigate later disease, as has been suggested in times past by clinicians who said that healed tuberculosis, by the blocking of lymphatics, reduced the spread of cancer and the toxic effect of empyema. More information on this problem would be welcome, and the higher survival rate among this group of miners, together with the lower incidence of lung cancer among coal-miners reported by Kennaway and Kennaway,[9] certainly points to the usefulness of further inquiry into the factors which may be responsible.

[1] Abbey Smith, R., *Brit. J. industr. Med.*, 1959, **16**, 318.
[2] Taylor, A. B., and Levi, J. M., *Annual Cancer Report, United Birmingham Hospitals*, 1954, **2**, 14.
[3] Bignall, J. R., and Moon, A. J., *Thorax*, 1955, **10**, 183.
[4] James, W. R. L., *Brit. J. industr. Med.*, 1955, **12**, 87.
[5] Buchberg, A., Lubliner, R., and Rubin, E. H., *Dis. Chest*, 1951, **20**, 257.
[6] Kergin, F. G., *J. thorac. Surg.*, 1952, **24**, 545.
[7] Nohl, H. C., *Thorax*, 1956, **11**, 172.
[8] Ballantyne, A. J., Clagett, O. T., and McDonald, J. R., ibid., 1957, **12**, 294.
[9] Kennaway, E. L., and Kennaway, N. M., *Brit. J. Cancer*, 1953, **7**, 10.

KING GEORGE'S JUBILEE TRUST APPEAL

In 1935 a grateful people subscribed £1m. as a national thank-offering for the twenty-five years' reign of King George V, and the offering was dedicated to the cause, always dear to the king's heart, of advancing the physical, mental, and spiritual welfare of the younger generation in his kingdom. The fund inaugurated for this purpose—King George's Jubilee Trust—is now celebrating its own silver jubilee, and it has just launched its first national appeal for funds since its foundation. Over the past twenty-five years the Trust has given more than £1m. in grants for the welfare of the young, but the income at the council's disposal, even with the help of legacies and other gifts, barely exceeds £40,000 a year. The funds are chiefly used to help those who leave school at the age of 15: there were 610,000 of these in 1948, and there will be 852,000 in 1961 and 927,000 in 1962. With the increasing calls upon it, the Trust needs an additional income of £110,000 a year.

Many of the Trust's grants are well known: it gives bursaries, for example, to enable young people who could not otherwise afford to do so to join the Outward Bound Trust courses at sea and mountain schools; to the British Schools Exploring Society; or to the courses on the old sailing ship *Foudroyant*, moored in Portsmouth harbour. It also gives a great deal of unseen support to the day-to-day work of the national voluntary youth organizations. As the Trust's council says, the appeal is a national appeal in support of a national cause, and it is described as a call to the nation to accept again as it did in 1935 its responsibility for those on whom the future of the country will depend. Those who are interested in the work of this very practical organization should send their inquiries to the secretary, King George's Jubilee Trust, 166, Piccadilly, London, W.1.

The Queen has conferred the Order of Merit on Sir Cyril Hinshelwood, President of the Royal Society and Dr. Lee's Professor of Chemistry in the University of Oxford.

Clinicopathological Conference

COMPLICATIONS OF ASBESTOSIS

DEMONSTRATED AT THE
POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with asbestosis with a fatal complication (Case No. 215526; P.M. No. 8556). He presented with haemoptysis, and exemplified the problems of diagnosis of the cause of haemoptysis and the nature of the lung changes associated with the asbestosis.

Clinical History

Dr. PHILIP HUGH-JONES: This man was aged 50 years at death. His medical history starts in 1922, when at the age of 14 years he got rheumatic fever. He apparently made a good recovery from this. However, he was graded in group IV at an Army medical examination in 1940 at the age of 32, though he himself felt perfectly well. In 1943 he had a gradual onset of swelling, aching, and stiffness of the metacarpophalangeal joints of both hands and of the wrists, shoulders, knees, and ankles. This continued for five years; there was little constitutional upset, but the illness left him with a residual stiffness of his shoulders and wrists and with deformity of the hands typical of rheumatoid arthritis.

From 1938 to 1949 he worked in an asbestos factory. There he felt well, but on routine radiological examination of his chest in 1949 he was told he had asbestosis, was certified, and subsequently became a storeman. From that time onward he noticed increasing shortness of breath on exertion. In May, 1958, he got worse, had a brisk haemoptysis, and was admitted to Hammersmith Hospital for investigation.

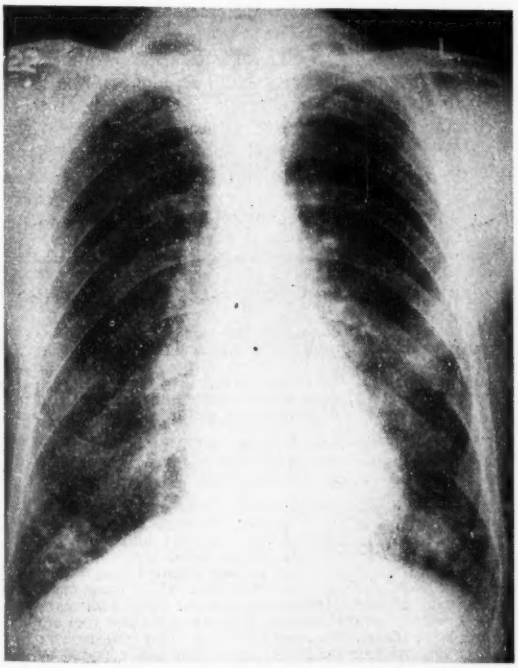

FIG. 1.—Chest radiograph (posterior view) on first admission. The fracture of the sixth rib is not visible.

EXAMINATION AND INVESTIGATIONS

He had marked clubbing of the fingers and toes; rheumatoid changes in his hands, elbows, and shoulders; enlarged axillary glands; and two small, mobile, cutaneous nodules on the medial side of the right arm. There were persistent scattered rales over both lungs. His blood-pressure was 120/65, his pulse was regular, and he had a grade 3 aortic systolic murmur, an accentuated pulmonary second sound, with an opening snap and mid-diastolic murmur at the heart apex. A radiograph of the chest (Fig. 1) showed a fracture of the sixth rib on the right, large pulmonary vascular shadows, and a reticular mottling over the lower zones of both lung fields, with a "shaggy" outline to the heart. On barium swallow there was slight enlargement of the left atrium. The changes at the right hilum could be those of an enlarged pulmonary artery, or those associated with a right hilar neoplasm. Tomography (Fig. 2) confirmed the right hilar mass.

His sputum was examined on numerous occasions for tubercle bacilli, malignant cells, and asbestos bodies, but nothing abnormal was found. Bronchoscopy showed the left-hand side of the bronchial tree to be normal. The right upper lobe was normal, but there was blood-stained mucopus in the region of the right middle lobe, with a granular appearance of the right descending and lower lobe bronchi. However, a biopsy from the granular areas showed no evidence of malignant change. Biopsy of lymph glands and of the skin nodules showed only changes compatible with rheumatoid arthritis.

The electrocardiogram gave little support for the clinical diagnosis of mitral stenosis, despite the slight enlargement of the left auricle seen on barium swallow. The blood count was normal except that the haemoglobin was 11.5 g./100 ml. Blood cultures were persistently negative. The E.S.R. was 125 mm./hour. The differential agglutination test was positive for rheumatoid arthritis, and electrophoresis of the serum proteins showed high α_2 and β peaks.

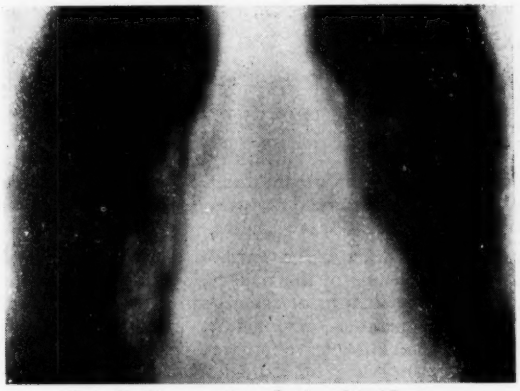

FIG. 2.—Tomograph confirming right hilar mass.

Lung function tests showed the changes typical of an interstitial fibrosis giving rise to alveolar-capillary block—namely, a reduced carbon-monoxide diffusing capacity, high exercise ventilation with arterial oxygen desaturation on exercise, a small inspiratory capacity, a maximum breathing capacity of 53 litres/min., which was large relative to the vital capacity, and a forced expiratory volume in 1 second (F.E.V. 1.0) forming a high proportion of the vital capacity (F.E.V.% =73).

SUBSEQUENT COURSE

During his stay in hospital the haemoptysis steadily decreased and he put on weight. He was assessed as having rheumatoid arthritis, rheumatic heart disease (mitral stenosis and aortic incompetence), and asbestosis, with probably an associated bronchial neoplasm. However it was conceivable that the haemoptysis could be associated with the mitral stenosis, that he had had a pulmonary artery thrombosis, or that it came from bronchiectasis associated with the asbestosis. In any event, further investigation seemed unjustified, for it was unlikely to alter treatment as the suspected bronchial neoplasm would be inoperable. He was therefore discharged to await progress.

Readmitted in August, 1958, his haemoglobin was 10 g. Chest radiograph (Fig. 3) showed markedly

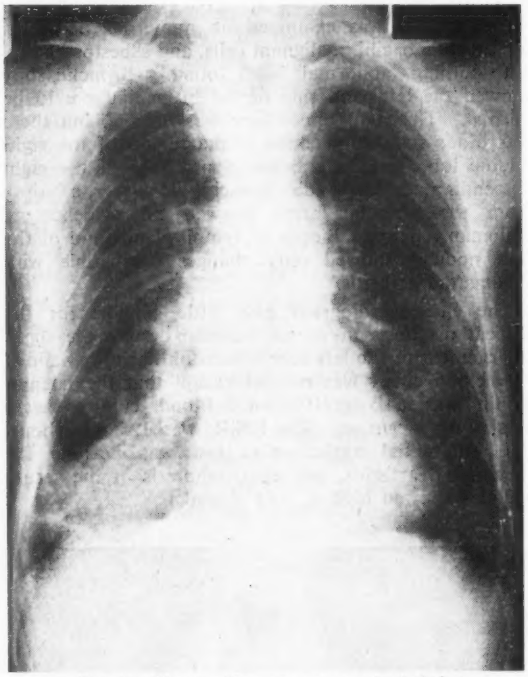

FIG. 3.—Chest radiograph on second admission.

increased shadowing on the right, with collapse of the tenth thoracic vertebrae. Again sputum examination for malignant cells was negative.

During this time in the ward he had two attacks of involuntary jerking of the right leg which were thought to be possibly a form of Jacksonian fit associated with a cerebral metastasis from lung carcinoma, though E.E.G. examination gave no positive support to this diagnosis. In view of the radiological findings the diagnosis of lung cancer associated with the asbestosis was much more certain, and, after transfusion, he was again discharged. After that he deteriorated steadily with increasing haemoptyses, though he was in no pain. He was finally admitted again in September, 1958, when he showed signs of consolidation of the right chest and a swelling over the left clavicle. He died on September 29.

Clinical Diagnosis

1. Carcinoma of right lower lobe bronchus, with metastases to spine, brain, and elsewhere.
2. Asbestosis.
3. Rheumatic heart disease (quiescent aortic incompetence and mitral stenosis).
4. Rheumatoid arthritis.

Post-mortem Findings

Dr. B. E. HEARD: The body was wasted: weight 6 st. 10 lb. (42.6 kg.), height 5 ft. 7 in. (1.68 m.). Both hands showed ulnar deviation and the fingers and toes were clubbed. There were two small nodules 1 cm. in diameter over the right elbow and there was one 4 cm. in diameter over the left. They contained caseous material and histologically showed inactive-looking fibrous walls lined by macrophages and enclosing amorphous material with many cholesterol clefts. There was no certain evidence of active rheumatoid disease here. The chest measurements were: antero-posterior diameter 20.5 cm., lateral 25 cm., circumference 72 cm. This is within the normal range and excludes a barrel-shaped chest. Both *pleural sacs* were completely obliterated by dense fibrous adhesions. The *pericardium* was also obliterated and showed a plaque of calcification over the pulmonary conus. The *peritoneum* was normal.

STATE OF THE LUNGS

The *trachea* and *main bronchi* contained a large quantity of blood-stained mucus and both lungs were oedematous. There was bronchiectasis in the fibrosed areas to be described. The *right lung* weighed 1,370 g. (normally 400–450 g.). There was a carcinoma 7 cm. in diameter in the posterior basal segment of the lower lobe adherent to the diaphragm and invading it. The cut surface was pale and granular and there was central necrosis. The lower lobe also showed some subpleural fibrosis. There were secondary deposits in the hilar lymph nodes. The middle lobe was heavily infected, all bronchi being filled with mucopus and the

LEGENDS TO SPECIAL PLATE

FIG. 4.—The left lung showing honeycombing of the anterior parts of the lingular and anterior segments of the upper lobe, and also of a thick subpleural zone commencing half-way down the back of the lower lobe and involving the costophrenic angle and the whole of the diaphragmatic surface.

FIG. 5.—A higher magnification (×1.4) of the left lower lobe, showing the subpleural zone of honeycombing and dense overlying adhesions.

FIG. 6.—A higher magnification (×1.4) of the postero-apical segment of the upper lobe to show a little apical scarring, a bulla (marked by an arrow), and numerous black foci of centrilobular emphysema, separated from septa (and veins) by zones of unpigmented lung at the periphery of each lobule. The fine white lines mark the edges of secondary lobules and the black foci mark their centres approximately. Between septa and foci are peripheral zones of unpigmented lung. Two pale deposits of carcinoma near the top of the picture are indicated by arrows.

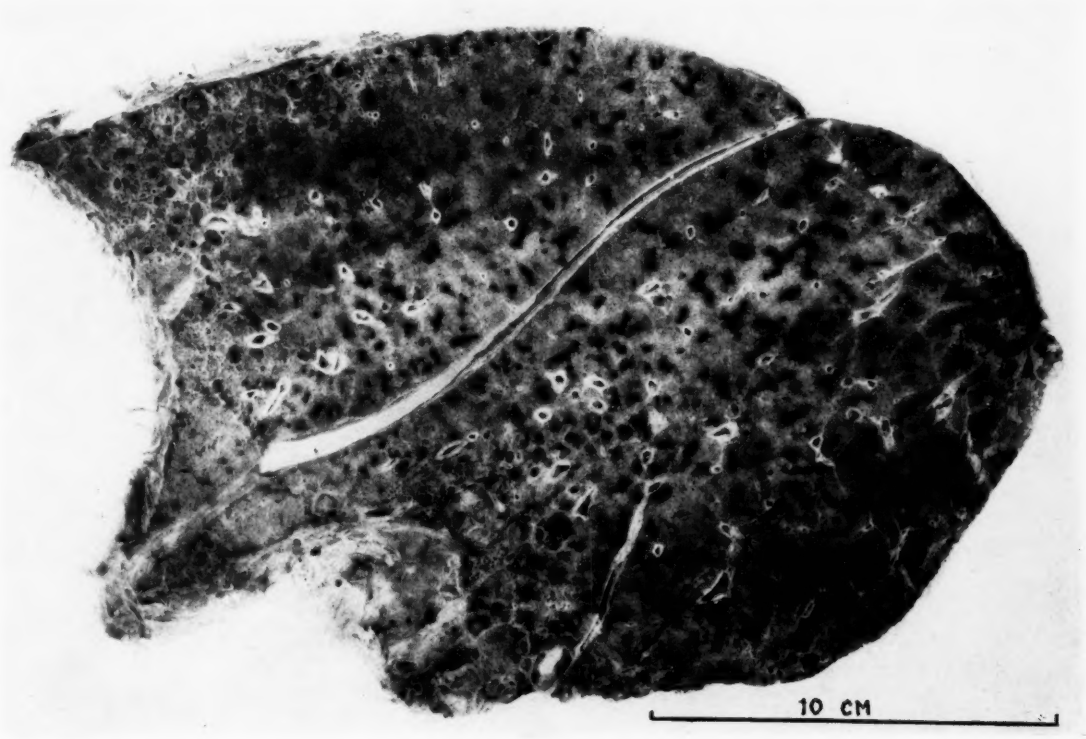

FIG. 4

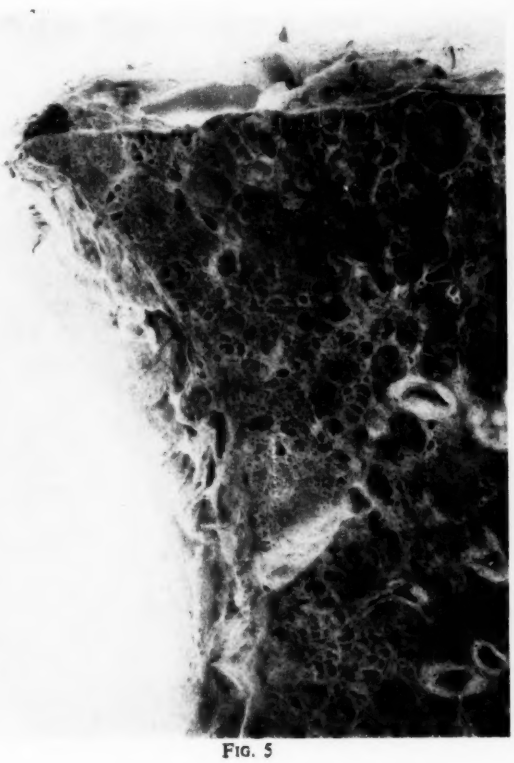

FIG. 5

FIG. 6

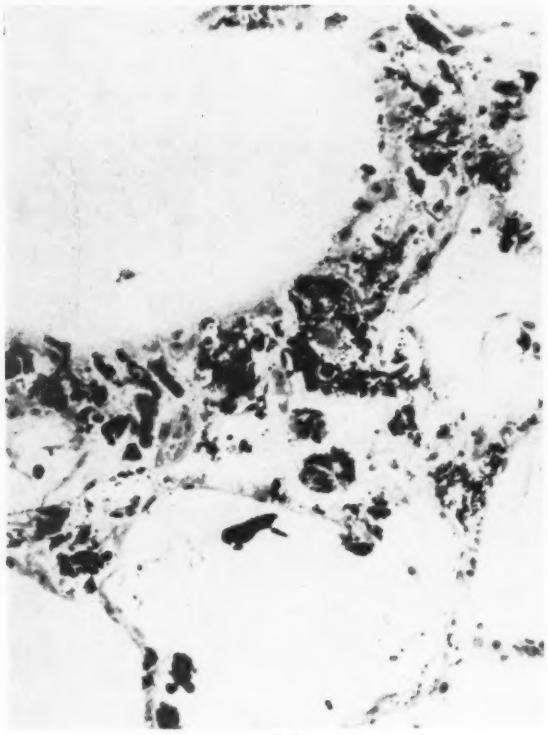

FIG. 7

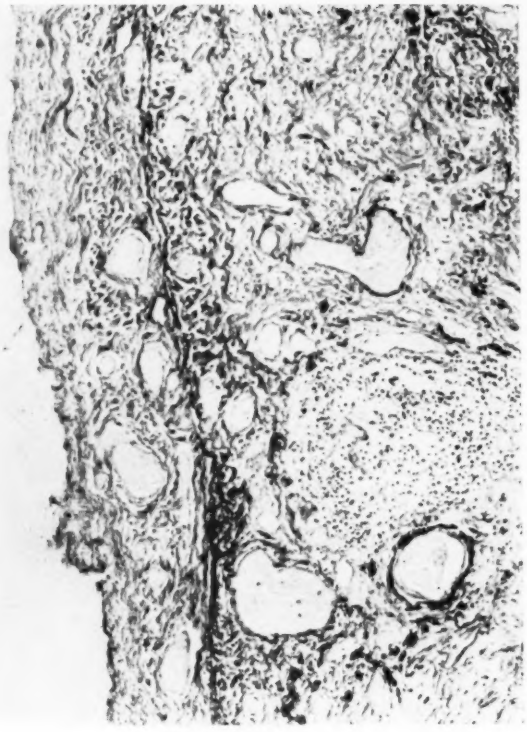

FIG. 8

FIG. 9

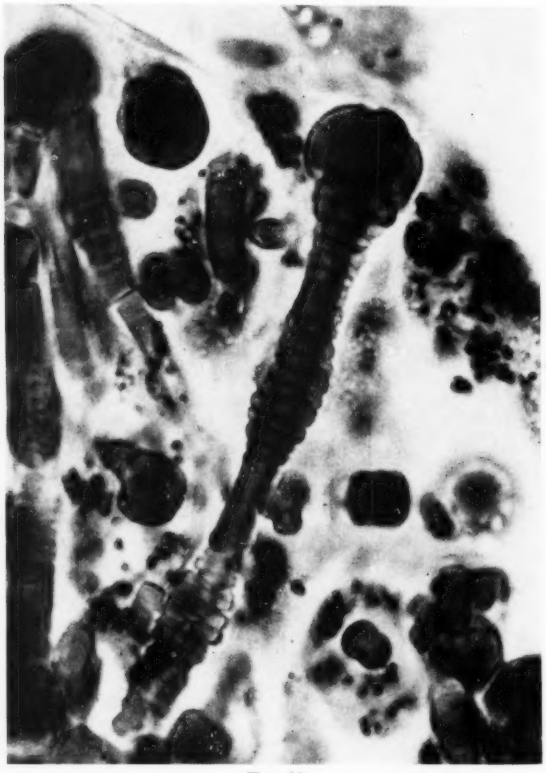

FIG. 10

lung yellow and consolidated. There was some honeycombing of the anterior part of this lobe. The upper lobe showed slight apical fibrosis associated with two bullae 1.5 cm. in diameter, but no calcification. In all parts of the lung unaffected by fibrosis there was mild centrilobular emphysema. (The appearance in the left lung is shown in Figs. 4 and 6.) Respiratory bronchioles well away from the interlobular septa were heavily dust-pigmented and moderately dilated. Histologically these emphysematous foci were shown to be pigmented by black dust in macrophages lying mostly within the walls of the dilated respiratory bronchioles, and in the same situation were numerous small asbestos bodies. There was no notable increase of reticulin in these areas. The tumour was a moderately well-differentiated columnar-cell carcinoma with tubular and papillary patterns. Most reports stress the frequency of squamous carcinoma with asbestos, so the present case is somewhat unusual. There is no question of this being a mesothelioma. The *left lung* weighed 885 g., and was prepared by pressure fixation and barium sulphate impregnation* (Fig. 4) to demonstrate emphysema. The volume of the lung (2.2 litres) was at the lower limit of normal. There was honeycombing (Fig. 5) in a thick subpleural zone of lung commencing half-way down the back of the lower lobe, including the costophrenic angle and the whole of the diaphragmatic surface. Also honeycombed were the anterior parts of the lingula and a little of the anterior part of the anterior segment of the upper lobe. Honeycombing was accompanied by bronchiectasis.

Histologically the detail of the respiratory tissue was considerably simplified. Most of the airways consisted of small bronchi or bronchioles which were dilated (Fig. 7). There were no alveolated passages. Between the holes were thick walls of moderately dense collagen, lightly infiltrated in places by lymphocytes but as a rule having an inactive appearance. Stains for elastic tissue showed no alveolar shadows, most of the elastic being confined to the walls of blood vessels (Fig. 8). The larger arteries in the fibrous areas of lung showed considerable intimal fibro-elastosis, but elsewhere in the lung intimal thickening was only slight. Most of the dilated bronchi were lined by cubical or flattened epithelium, but in some areas macrophages were present in moderate numbers, sometimes accompanied by amorphous debris. Some of the macrophages were in the form of multinucleate giant cells (Fig. 9), well-known in recognized asbestosis. Asbestos bodies (Fig. 10) were lying free in the lumen, often in clumps. They had the characteristic golden-brown colour, and stained intensely for iron by Perls's reaction. Some of the bodies were smooth and rounded. Others were sausage-shaped with a variable amount of segmentation. Some sharp-ended crystals accompanied the bodies and may have been asbestos fibres. Elsewhere in the lung there was centrilobular emphysema of a mild grade.

The low volume of the lung and the encasing effect of the honeycombing correlate well with the lung-function studies, which showed a small inspiratory capacity. This may be what has been referred to as a "tight" lung. The adhesions were moderately dense over the lung but were not cartilage-like.† There was no evidence of Caplan's change despite the coincidence of rheumatoid arthritis and asbestosis as described by Rickards and Barrett.‡

*Heard, B. E., *Thorax*, 1958, **13**, 136; ibid., 1959, **14**, 58.

LEGENDS TO SPECIAL PLATE

FIG. 7.—A focus of centrilobular emphysema showing asbestos bodies with other pigment in the walls of dilated respiratory bronchioles. (×245.)

FIG. 8.—A section of a fibrosed juxtapleural zone stained to show elastic fibres. On the left is a thin layer of pleural fibrous tissue lying outside the elastic lamina which marks the original border of the lung. Within the lung, finer air spaces have been replaced by dense fibrous tissue. The minimal elastic content is related to small blood vessels. (×95.)

FIG. 9.—A multinucleate giant cell containing fragments of asbestos bodies. (×1,012.)

FIG. 10.—A clump of asbestos bodies showing wrinkled encrustations over the asbestos fibres. (×1,012.)

HEART AND OTHER ORGANS

The *heart* weighed 370 g. (normally 281–361 g. for a man of 5 ft. 7 in.—1.68 m.). The increase in weight was partly due to dense adhesions, described above, and partly to a trace of hypertrophy of the left auricle and possibly the right ventricle (L.V. 1.5 cm. thick, R.V. 0.4 cm. thick). The pulmonary and tricuspid valves were normal, but the mitral valve was 70 mm. in circumference (normally 90–110 mm.). The chordae tendineae were fibrous but not shortened. The edge of the valve was straight. The valve cusps were fused and thickened by fibrosis and the valve admitted one and a half finger-tips. Histologically there were no signs of active rheumatic fever, but at one point there was a small mural thrombus as described by Magarey,§ who attributes the fibrosis to the organization of successive layers of fibrin on the surface. The aortic valve was normal in circumference but showed adhesion of the commissures for distances up to 7 mm. The cusps themselves were slightly fibrosed. There were no vegetations. The coronary arteries showed moderate atherosclerosis and the aorta a mild degree. The heart changes were consistent with an old history of rheumatic fever. There was no sign, histologically, of rheumatic activity.

The *oesophagus* and the rest of the *alimentary tract* were normal, but the *liver* was slightly increased in weight (1,630 g.; normally 1,400–1,600 g.), and contained some scattered secondary deposits of growth up to 1 cm. in diameter. It showed centrilobular congestion throughout, confirmed histologically. The *gall-bladder, biliary ducts,* and *pancreas* were normal. The *spleen* was normal, but the bone-marrow of the sternum, ribs, and vertebrae contained numerous large secondary deposits. There was a fracture of the middle of the sternum and collapse of the tenth thoracic vertebra. The *adrenals* (right 15 g., left 20 g.; normally 6–7 g. each) were enlarged by metastases but the other endocrine glands were normal. The *genito-urinary* system was normal. The *brain* showed secondary deposits (Fig. 11) up to 1 cm. in diameter in the left occipital lobe and in both cerebellar hemispheres.

Pathologist's Diagnosis

1. Carcinoma of the lung with metastases in the hilar lymph nodes, adrenals, liver, brain, and bones.
2. Honeycomb lung due to asbestosis.
3. Old rheumatic heart disease.
4. Old rheumatoid arthritis.

†Gloyne, S. R., *Tubercle*, 1933, **14**, 445.
‡Rickards, A. G., and Barrett, G. M., *Thorax*, 1958, **13**, 185.
§Magarey, F., *Brit. med. J.*, 1951, **1**, 856.

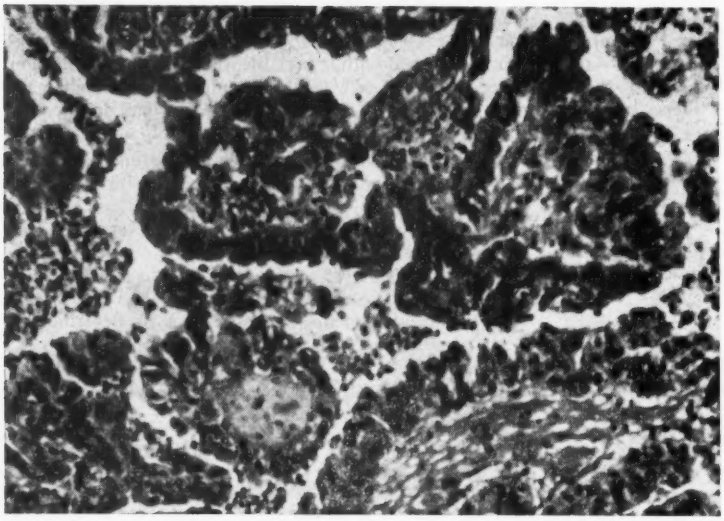

FIG. 11.—A cerebral secondary deposit of adenocarcinoma from the lung. (×153.)

Asbestosis Reviewed

Professor J. MCMICHAEL: Dr. Hugh-Jones, would you sum it up?

Dr. HUGH-JONES: The case is of great interest, as it demonstrates so many of the problems associated with asbestosis which we should review. Asbestos itself is chiefly a double silicate of magnesium and iron. It occurs in a number of mineralogical forms, one of the most valuable being chrysolite. Asbestosis is a pneumoconiosis arising from the inhalation of asbestos dust during the manufacture of asbestos goods, such as asbestos sheeting, fireproof clothing, brake-linings, lagging for boilers and pipes, etc.

One way of thinking of the pneumoconioses is in relation to the chemical toxicity of the different dusts. At one extreme are those, such as iron, which are entirely non-toxic and simply produce a characteristic radiological appearance of the lungs with no change in bodily function. Then come others, such as coal, which do this but also have a pathogenic action by altering the reaction of the lungs to tubercle. Next there are dusts, such as silica, which produce a local reaction in the lungs and pulmonary fibrosis. Finally there are others, such as beryllium, of such toxicity that they can be regarded as general tissue poisons, which produce widespread effects in the body as well as local fibrosis in the lungs. Asbestos is very toxic and produces not only pulmonary fibrosis but reactions in the pleura and even in other organs. Dr. Heard has excellently demonstrated the pathology of asbestosis in our patient, but by way of summary here is a picture (Fig. 12) of a whole-lung section of another patient who died from asbestosis. There is an interstitial fibrosis, as in the present case, gross pleural thickening, and some patchy bronchiectasis. Besides these three features, which are common in asbestosis, there may be associated tuberculosis, as there was in this second case, or, even more important, associated lung cancer, as in our patient. Sometimes the interstitial fibrosis gives rise to the formation of bullae, or occasionally even to a widespread "honeycomb lung"—i.e., that which occurs with other rare forms of pulmonary interstitial fibrosis, such as the xanthomatoses.

RADIOLOGICAL APPEARANCES

These are typically those of a fine lace-like reticular pattern, particularly affecting the lower lung fields and causing a "shaggy" border to the heart, as in our patient. Besides this, cystic changes may be seen and very often the pleural thickening. Although the *x*-ray picture is typical and almost pathognomonic in a few advanced cases, there are many patients who have undoubted asbestosis (as judged by a history of exposure and the clinical features of clubbing, rales in the lungs, and typical changes in lung function) who do not have specific changes in their chest radiograph. That is extremely important in relation to the diagnosis, as we shall see later, because in general the diagnosis of pneumoconiosis depends on an appropriate industrial history and a characteristic *x*-ray appearance. There is a characteristic *x*-ray appearance in asbestosis, but unfortunately from the medico-legal standpoint not all patients with asbestosis have the characteristic radiograph. Finally, the radiological appearances of asbestosis cannot be classified in the same categories as those accepted internationally for the other pneumoconioses.

CLINICAL FEATURES AND COURSE

Gross clubbing of the fingers and persistent rales in the chest are the characteristic clinical signs of the condition. Exertional dyspnoea is the main symptom, as in other pneumoconioses. Patients suffering from

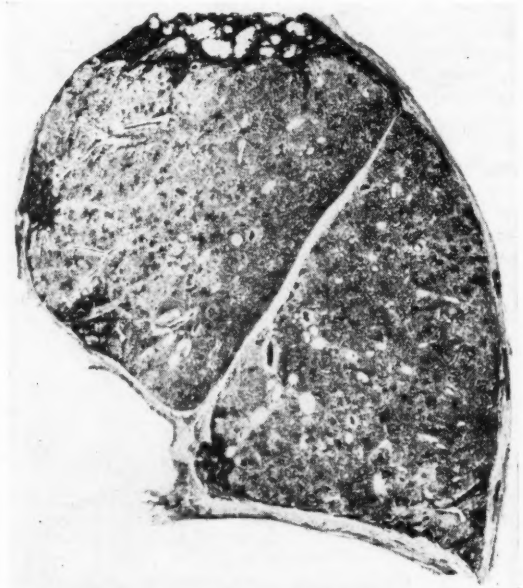

FIG. 12.—Large lung section, prepared by Professor Gough's technique, from another patient with asbestosis, showing the gross pleural thickening, patchy fibrosis, and bronchiectasis, and accompanying tuberculosis at the lung apex.

asbestosis may die either from the complication of tuberculosis (more common in past years), or more particularly from that of carcinoma of the lung. Those not killed by chest infection or cancer may finally get cor pulmonale.

The disease usually makes its appearance rather suddenly, over the course of a few months, often long after the initial exposure to the asbestos inhalation. It has been suggested that the asbestos lies dormant as an asbestos body, which has to "ripen" over many years before it can break down and liberate its toxic contents. In this respect asbestos is again like beryllium, which may also lie dormant in the body and then suddenly produce its effects concurrently with some other infection.

Carcinoma of the lung is a serious and well-recognized complication in asbestosis. Its frequency in asbestosis is difficult to determine, for it is now a common condition in the general population. Moreover, exposure to asbestos may have occurred many years before the cancer develops. Nevertheless, the paper by Doll‖ makes it fairly clear that a patient with asbestosis has a risk about 10 times that of the general population of getting carcinoma of the lung. Another hazard is mesothelioma of the pleura. This rather rare tumour may draw attention to the fact that a patient has worked in asbestos dust. Finally, in women who work with asbestos there is a high incidence of cancer of the ovary.

Functional Effects

There is a diminution of the inspiratory capacity which fits in with the "shrunken lung" demonstrated by Dr. Heard in this case. In contrast with other pneumoconioses there is often little disturbance to air flow, so that all the movement of the lungs there is is used to good advantage, and the maximum breathing capacity (M.B.C.) is often surprisingly well maintained. Thus if a patient suffering from asbestosis is assessed by the M.B.C. or forced expiratory volume (F.E.V.) test, he is unfairly assessed for compensation compared with a man suffering from silicosis or coal-workers' pneumoconiosis. The essential cause of the breathlessness in asbestosis is the difficulty of transference of oxygen across the altered alveolar membrane, more so than the reduced maximum breathing capacity, which is the cause in, say, coal pneumoconiosis. Carbon dioxide, being soluble, diffuses 20 times as rapidly as oxygen and is unaffected. Oxygen transfer is usually adequate at rest, so that the patients are rarely cyanosed, but when they start to exercise there is a rapid fall in oxygen saturation and gross hyperpnoea.

The diagnosis is made on a history of exposure, the presence of clubbing and rales, and usually by means of a radiograph. There is, however, evidence that the radiograph may not show changes as early as do the lung-function tests. Although the latter are not specific to asbestosis, they are only seen in other uncommon diseases which cause alveolar-capillary block and interstitial fibrosis (such as sarcoid, scleroderma, microlithiasis, and other rare conditions). Thus lung-function tests are useful for making the pathological diagnosis, for, if it can be shown that the patient has an interstitial fibrosis causing alveolar-capillary block, has gross clubbing and rales, and a history of exposure to asbestos dust, it seems reasonable that he has asbestosis whether the radiograph is specific or not.

‖Doll, R., *Brit. J. industr. Med.*, 1955, **12**, 81.

Asbestos Dust

The asbestos bodies simply prove exposure to asbestos dust and of themselves do not mean asbestosis. Anyone may cough up asbestos bodies who has inhaled dust, without necessarily having the changes of asbestosis in the lungs. Vice versa, a patient may have definite and gross asbestosis without asbestos bodies necessarily being found in the sputum during life. Since, medico-legally, the diagnosis depends on a history of dust exposure together with the appropriate *x*-ray and other changes, the finding of asbestos bodies is of importance in proving exposure.

It seems probable that asbestos fibres, once inhaled, are coated with collagen. Over the course of years the collagen cover "ripens" by forming transverse cracks, and then the asbestos body can break down, liberating the toxin and causing the reactive fibrosis in the lungs. The nature of the toxin is uncertain. It is, however, presumably the same substance which is carcinogenic.

Asbestosis was first described in this country by M. Murray in 1907. After that, in 1930, Mereweather and Price¶ reported the dangers of asbestos dust in the lungs and made recommendations for dust suppression. Thereafter there was a great improvement. In the factory where our patient worked the utmost precautions are now taken to prevent asbestosis occurring. It is a disappearing disease. Nevertheless, asbestos dust is most toxic, and the amount needed to cause asbestosis is not known, so constant vigilance and new preventive methods are needed if this disease is to be abolished.

Discussion

Professor McMichael: There are many other facets to this patient, but before we go on to them are there any other points or queries which could be raised on the pathogenesis of asbestosis?

Dr. R. S. Williams: I think there is one point in support of the mechanical theory that is worth raising. If experimentally you give asbestos ground up into a fine dust, fibrosis does not occur, and it seems that asbestos fibres between 20 and 50 microns in length are necessary to produce the typical peribronchiolar fibrosis.

Distribution of Fibrosis

Professor E. G. L. Bywaters: What is the explanation of the distribution of fibrosis? Does it correspond to the distribution of asbestos in the lung, or is there some other explanation?

Dr. Heard: As a matter of fact, it doesn't seem to correspond. Although some of the best asbestos bodies in this case were in fibrosed areas, there were plenty surrounded by perfectly normal lung in other parts. Dr. Nagelschmidt, from Sheffield, was here two days ago and he was saying that they have recently examined chemically a number of lungs from cases of asbestosis. In some there was a lot of fibrosis and practically no asbestos. However, he did point out that there was a possible error because the asbestos content was estimated as the percentage of the dried weight and the dried weight of fibrosed lung is not altogether comparable to the dried weight of the normal lung. It is quite a problem, and, so far as I know, the peripheral distribution of the fibrosis has not been explained. It is not restricted to asbestosis, being seen in other forms of honeycomb lung.

¶Mereweather, E. R. A., and Price, C. W., *Report on Effects of Asbestos Dust on the Lungs*, 1930. H.M.S.O., London.

ASBESTOS IN THE PERICARDIUM

Professor MCMICHAEL: Dr. Plotz, you have a question?

Dr. PLOTZ (New York): I've got a couple of questions. In reading the case history I was surprised—pleasantly surprised and greatly relieved—to find that no mention was made of this man's smoking habits. Some of our surgical friends are putting asbestos rather than talc into the pericardial cavity to produce adhesions, on the grounds that chemically they are both silicates and the adhesions grow much more quickly with asbestos. This does not meet with my approval on other grounds, but I am wondering what Dr. Hugh-Jones and Dr. Heard would have to say about that. One other minor point that bothered me a little in the case history—perhaps I am getting a little touchy at the age of 50 and a little over—but you said that his age was a factor in determining whether or not to operate on him, and you decided not to operate on him because of his age. I am wondering if he was too old, or too young.

Dr. HUGH-JONES: I couldn't agree with you more about age. But the thing we debated in his particular case was the patient's general condition, including his age. He was a man of 50 who had gross rheumatoid arthritis and was considerably disabled and deformed by it. He had severe breathlessness from his asbestosis, and his general condition was such that we didn't think it was justifiable to do an exploratory thoracotomy on a very small chance of being able to eradicate the carcinoma permanently. I am afraid I am not all that optimistic about the effects of surgery in carcinoma of the lung.

He did smoke, but incidentally he had an adenocarcinoma, which is not a kind particularly related to smoking so far as one knows. We believe, from the work that is being done both in this country and in the United States in relation to smoking, that it is the squamous and the oat-cell carcinomas which have arisen since the 1900s and could be correlated with smoking. Way back in the 1900s carcinoma of the lung was equally common in men and women, and it was predominantly an adenocarcinoma then. It is the recent emergence of the squamous and oat-cell types which gives the male preponderance and which various people have related to smoking.

Professor MCMICHAEL: What about the dangers of asbestos in the pericardium?

Dr. HUGH-JONES: I think that's a very interesting point, because asbestos and talc are similar chemically. On general principles I would be a little worried about the possible ultimate effects of asbestos in the pericardial cavity. Talc is used in the pleural cavity to produce adhesions after many spontaneous pneumothoracies, but I don't know if anyone has put asbestos in the pleural cavity. I would be a little worried about asbestos, but I've got no reason for saying that it's a bad thing.

Dr. C. L. COPE: Is there any lung trouble in talc manufacturers?

Dr. HUGH-JONES: Oh, yes.

RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

Professor MCMICHAEL: Professor Bywaters, would you like to comment on the recurring sequence of alleged acute rheumatic fever followed by progressive rheumatoid arthritis? This is the second example we have seen to-day.

Professor BYWATERS: I think they are both fairly common diseases. And when you get a difference here of, say, 21 years between the two, with the rheumatic fever occurring in childhood, I think a coincidence is possible. We have seen a number of people with both diseases, and one disease doesn't seem to confer immunity from the other. I think we are always happier that the first diagnosis is correct when there are no intervening symptoms. Here there is no doubt about the rheumatoid arthritis. I didn't see the patient during life, nor I think did Dr. Dixon, so I am not quite happy about the nodules which Dr. Hugh-Jones described. It's a very unusual place he pointed to on his own arm.

Dr. HUGH-JONES: That was where they were on this patient's arm.

Professor BYWATERS: I would think it's quite likely that they weren't rheumatoid nodules. Dr. Heard didn't seem any too happy either on the pathological side, but I haven't seen the sections. I think this is of some importance from the point of view of the lung, because the Caplan type of lesion seems to occur mainly in rheumatoid patients with nodules elsewhere. In fact the Caplan lesion is a modified rheumatoid nodule occurring in the lung substance or the pleural fissures, perhaps as a result of the abnormal stresses from fibrosis. You can trace in early specimens the pallisade layer round the necrotic fibre which is the hallmark of the rheumatoid nodule. I am not saying that these are not nodules, I haven't seen them; but it might be the reason why he didn't develop further changes in his lungs.

Professor SHEILA SHERLOCK: When I first came to this School in 1942 I used to sit back admiringly while Professor Bywaters thought of another good reason why rheumatoid arthritis and rheumatic fever were unrelated diseases. Is there really no relation between these diseases?

RHEUMATOID ARTHRITIS AND DISSEMINATED LUPUS

Dr. COPE: I've commented at a previous conference on the relative frequency with which we've seen acute rheumatism followed by rheumatoid arthritis and then followed by disseminated lupus. When somebody wrote to me about this and inquired for details I quoted the two cases I knew of, and the same day, whilst I was doing the letter, the Records Department turned up five others which were diagnosed "rheumatoid arthritis" and then subsequently disseminated lupus.

Professor BYWATERS: We feel there is no real relation but often close clinical, and sometimes even pathological, similarities. Unless you have got bona-fide heart lesions, it is sometimes extraordinarily difficult to differentiate the early stage of rheumatic fever from the very early episodes of lupus, ankylosing spondylitis, or rheumatoid arthritis. If you get adequate heart lesions, you can be fairly certain about it sometimes!

Professor MCMICHAEL: It's very interesting to see these "arrested" valvular lesions. The minimal adhesion of the mitral valve and aortic valve cusps indicates that, even although the valves may be damaged, progression is not inevitable. There are some who think that progression of rheumatic valvulitis is inevitable, but this man, presumably with valve damage at 14, got through to 50.

FRACTURED RIB

Professor BYWATERS: Was there any evidence at necropsy of any metastasis in the fractured rib that might have given us an earlier clue to the diagnosis?

Dr. HEARD: There were very widespread metastases. I didn't examine that particular rib, but I expect it was affected.

Dr. COPE: What about this heavy intimal thickening, is it characteristic of asbestosis? Does it lead to pulmonary hypertension, or what happens?

Dr. HEARD: The gross intimal thickening of the pulmonary arteries that I showed was in the fibrous areas. Elsewhere there was only a little thickening. With this and the normal right ventricle, I doubt whether there was much in the way of pulmonary hypertension here.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

Drug Treatment of Disease

INFECTIONS OF THE EYE

BY

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Infections of the interior of the eye are grave emergencies and call for immediate and expert treatment. Relatively uncommon, they are seen after intraocular operations, perforating injuries, or in severe infections of the cornea. In contrast, infections of the outer eye are of daily occurrence. When the infection is bacterial in origin, treatment by antibiotics is generally efficacious, but virus infections still present a considerable problem.

The poor penetration into the interior of the eye of many of the antibiotics greatly limits the value of systemic administration of these drugs in the treatment of intraocular infections. Fortunately, subconjunctival injection of some of the antibiotics is a feasible procedure in expert hands and gives excellent results. For the external infections of the eye, local application is so eminently satisfactory, and so readily given, that neither systemic administration nor subconjunctival injections often need to be considered. The newer agents thus carry forward an older tradition of both ophthalmology and dermatology, in which local applications have always had a greater vogue than systemic therapy.

AVAILABLE DRUGS

Sulphonamides

The classical sulphonamides are all highly insoluble. When sulphacetamide as a soluble sodium salt became available it was used widely as a local application in all forms of ocular infection, including infected corneal ulcers. Some of the claims put forward for sulphacetamide were untenable; the experimental and clinical results claimed for corneal infections due to *Pseudomonas pyocyanea*—organisms insensitive to sulphonamides—merely reflect the early and rather uncritical enthusiasm for the sulphonamides. It may be taken that the limited range of action of the sulphonamides, together with the fact that the sulphonamides locally are inactivated by pus and breakdown products of tissue, make sulphacetamide of little value in ocular therapeutics.

There is, however, an unquestioned place for the sulphonamides given systemically in treating some of the external infections of the eye; in ophthalmia neonatorum it is possibly still the agent of choice. The causative organism in ophthalmia neonatorum is commonly *Staphylococcus aureus*; a virus closely allied to that of trachoma is responsible for another substantial group in which inclusion bodies can be found in epithelial scrapings taken from the conjunctiva; the gonococcus accounts for a relatively small proportion of the total—possibly as little as 20% or less in present-day series—and the pneumococcus accounts for a further substantial proportion. All these organisms are fairly readily susceptible to the modern sulphonamides in adequate concentration, so that most cases of ophthalmia neonatorum respond quickly to systemic administration.

Apart from ophthalmia neonatorum, and the somewhat similar purulent ophthalmia of adults, the sulphonamides systemically are useful in the after-treatment of septic affections in the lid and orbit dealt with surgically. In the treatment of intraocular infections the sulphonamides systemically are of little use owing to their poor penetration.

Sulphonamides administered locally are of value in only one disease: trachoma free from secondary infection. It is, however, likely that this isolated indication for the use of sulphacetamide has already been superseded by the greater efficacy of some of the antibiotics.

Antibiotics for Systemic Administration

Penicillin, streptomycin, chloramphenicol, and the tetracyclines are widely used systemically, and are all valuable as local applications in ophthalmology. The extensive use of penicillin ointment as a prophylactic measure after removal of corneal foreign bodies and after other minor injuries of the eye has greatly reduced the incidence of infected corneal ulcers and mucopurulent conjunctivitis. Ointments of penicillin and of chloramphenicol, as also of tetracyclines, are used commonly in the treatment of subacute and acute conjunctivitis, and of blepharitis, replacing almost entirely all the older remedies. Penicillin and streptomycin, being very soluble, can also be used as subconjunctival injections for infected corneal ulcers and intraocular infections generally, so that there is a broad field for the use of these agents in ophthalmology.

Recently it has been questioned whether it is justifiable to give any of these antibiotics for relatively minor infections. It is held that some patients may become sensitized, making the systemic administration

of the drugs hazardous in a future emergency. There is also the possibility of these agents producing local sensitization, so that local reactions are precipitated from subsequent systemic use, even if no severe systemic effects are observed. Though there is some question whether local application of an antibiotic can precipitate generalized sensitization, there is little doubt that local sensitization is a real problem. In consequence, there is at present a tendency to limit the local application of such antibiotics as are also given systemically. This tendency has been strengthened by the fact that penicillin-resistant *Staph. aureus* and Gram-negative bacilli are now so frequently present in infections of the eye that in any case it is questionable whether some other antibiotics more suitable to present-day conditions would not be better. It is for these reasons that considerable attention has been given of late to antibiotics that are used exclusively as local applications and have a wide spectrum.

Antibiotics for Local Administration Only

The outstanding antibiotic in this group is neomycin. It has an exceptionally wide range of action on bacteria, including penicillin-resistant *Staph. aureus* and many Gram-negative bacilli, among them many strains of *Ps. pyocyanea*. It is not particularly effective against the pneumococcus, but in the concentrations applied locally this limitation is not apparent. The polymyxins, too, are useful, but they are highly specific to some strains of *Ps. pyocyanea*, with little effect on other organisms, and are therefore to be used only against an organism known to be susceptible. Recently framycetin ("soframycin"), with a range of action almost approaching that of neomycin, has also received much attention; it is not effective against most streptococci nor against *Dilococcus pneumoniae*, two strains commonly met with in ocular infections. Bacitracin has also a fairly wide range of action, being effective against Gram-positive and Gram-negative cocci and most Gram-positive rods; it is, however, without effect on the common Gram-negative bacilli. For this latter reason bacitracin is generally used in combination with polymyxin. The exact possibilities of these various antibiotics still require critical assessment, but it would seem that neomycin ointment 0.5% can usefully replace most of the antibiotic preparations being applied locally.

Antibiotics and Corticosteroids

The specific therapy possible with the antibiotics calls for specific diagnosis—that is, it is necessary not only to establish that there is infection, but, where possible, to assess the nature of the infection on clinical or bacteriological grounds. This is particularly important for any reaction which does not readily respond to antibiotic therapy, for it is likely that the wrong drug is being given. To use the antibiotics with their specific effect on tissues that are merely inflamed and not infected is both irrational and ineffective. Antibiotics do not control an iritis, which is an inflammation of the eye, nor glaucoma with its inflammatory reactions; nor do they control allergic reactions of the lids, conjunctiva, or interior of the eye, for here again there is no infection. The inflammatory diseases of the eye are a complex chapter, and gratifying results can sometimes be obtained by the use of the corticosteroids.

To combine the corticosteroids with an antibiotic, as is a common practice, is to convert two useful agents into one bad compound and to indulge in blunderbuss therapy of a particularly objectionable type. Infections are readily controlled by suitable antibiotics and do not require corticosteroids, the use of which may in fact hinder recovery by spreading such infection as is not controlled. Likewise inflammatory reactions of non-infectious origin, which can be controlled by corticosteroids, do not need antibiotics, whilst such inflammatory reactions as are not controlled will not be influenced by antibiotics, which may add their own quota of irritability to an already damaged tissue. There are indeed rare instances in which an inflammatory reaction also shows secondary infection; here the combined use of the two agents by an expert may be justified.

CLINICAL APPLICATIONS

1. Bacterial Infections of the Outer Eye

Ophthalmia Neonatorum

Treatment can be either by the sulphonamides systemically or by penicillin locally. Sulphonamide therapy is less exacting on the nurse, while treatment with penicillin gives more rapid control. Occasionally the two methods need to be combined in a slowly yielding case; there is, however, no need to use these procedures in combination as a routine. Whichever method is used, a swab is taken for bacteriological examination, the eye is irrigated with some bland lotion, such as half-normal saline at room temperature, and, where facilities are available, a drop of adrenaline 1 in 1,000 is instilled and a scraping of the palpebral conjunctiva is taken for examination for the presence of inclusion bodies. In all cases a drop of atropine sulphate 1% is instilled, followed by a drop of medicinal paraffin. The subsequent management differs with the two methods.

Sulphonamide Therapy

(1) A tablet (0.5 g.) of sulphadimidine, or of sulphamerazine, crushed into powder is given by mouth in a teaspoonful of water or milk. Alternatively a stock mixture can be used.

(2) Sulphadimidine in doses of 0.25 g. is continued every six hours. If sulphamerazine is used the administration has to be at intervals of eight hours.

(3) Local treatment, during the first day in cases with profuse discharge, consists of irrigation every three hours with saline solution; as a rule there is no need for further irrigation on the subsequent days. After irrigation medicinal paraffin is instilled as a precaution against the sticking together of the lids.

(4) The sulphonamide is continued for 48 hours after clinical cure.

With this treatment swelling of the lids generally subsides within 12 hours of beginning treatment; purulent discharge disappears within 24 hours. Cases due to the virus of inclusion blennorrhoea respond as readily as those due to bacteria.

Penicillin Therapy

(1) The preliminary measures are completed by the instillation of a drop of penicillin in a concentration of 10,000 units per ml. into the conjunctival sac.

(2) The baby is now placed on the nurse's lap, while another nurse sitting near by instils one drop of penicillin solution, 10,000 units per ml., into the conjunctival sac every minute for 30 minutes. Irrigation is not needed, as pus does not form to any extent. Such thin mucoid discharge as is present can be ignored, or, if it clings to the lid margin, wiped away with moist pledgets of cotton-wool.

(3) At the end of this time there is invariably no pus and generally little or no discharge. The eye, however, is still moist, the lids are still swollen, and the lid margins tend to be sticky. The baby is returned to its cot, and instillation of penicillin drops is continued six times at five-minute intervals, followed by a similar number of instillations at intervals of half an hour, one hour, and two hours. This gives a total of 22 hours' treatment. Many cases require no further attention.

(4) In some babies the lid margins still tend to remain sticky. It is advisable in such cases to continue with penicillin at intervals of two hours until the eye is dry, when treatment is carried on for a further 12 hours.

With either method severity itself is not a significant factor in the duration of treatment. Frequently, mild cases take longer to clear than do moderate or severe cases, and equally often severe cases show remarkably gratifying response within a very short time, the sensitivity of the infecting organism rather than the severity of the reaction determining the course. With either treatment there are occasional cases with an unsatisfactory response in so far as moistness of the conjunctiva and sticky lid margins persist, and sometimes some oedema of the fornices or even a slight discharge. Such cases are best treated by changing the method or combining the two methods. When relapses occur, it is only exceptionally that the condition is as severe as it was initially, and it responds readily to a further course of treatment. Where corneal haze develops or a corneal ulcer threatens, expert advice should be sought.

Purulent Ophthalmia in the Adult

Local penicillin therapy differs in no way from that given for ophthalmia neonatorum. Systemic sulphonamide therapy is also as for ophthalmia neonatorum, except that full adult doses of the sulphonamide have to be given—for example, an initial dose of 2 g. of sulphadimidine or sulphamerazine with a maintenance dose of 1 g. at intervals of six or eight hours.

Muco-purulent Conjunctivitis

Most cases will respond to penicillin ointment 1,000 units per gramme, instilled at intervals of one to two hours for two to three days. In all cases it is advisable to take a smear for bacteriological control. If the clinical response is poor, some other antibiotic should be tried in the light of the sensitivity test: chloramphenicol ointment 1.0%, or one of the tetracyclines in ointment form of 0.5 to 1.0%, or an ointment containing 10,000 units polymyxin and 500 units bacitracin per gramme, or neomycin ointment 0.5% may be necessary. Sulphacetamide ointment, though widely used, is of limited or no value.

Blepharitis

In blepharitis, cleansing of the lid margins with some solution such as borax or bicarbonate lotion is still essential before applying ointments containing an antibiotic. Penicillin ointment 1,000 units per gramme applied three times a day is adequate in most cases, but ointments of either chloramphenicol (1.0%), the tetracyclines (0.5 to 1.0%), or neomycin (0.5%) will do as well. Some cases do better on painting of the lid margins with liquor tinctorium B.P.C. at night for a month or so.

2. Virus Infections

The greatest contribution chemotherapy and the antibiotics have made to ophthalmology probably rests with their effect on trachoma—the largest single blinding disease in the world as a whole. Local application of sulphonamides has proved a highly effective measure and there is now much evidence that chlortetracycline may give even more rapid results.

The following simple procedure in the management of trachoma has been found effective:

(1) Oral administration of full doses of sulphathiazole or sulphadimidine for 10 days.

(2) Mechanical expression of the follicles and of the contents of the fornix under local anaesthesia. Only rarely is brossage needed. If necessary, expression is repeated after 7 or 14 days.

(3) The conjunctival surface thus treated is painted immediately with 30% sodium sulphacetamide solution. Such painting is continued once daily, and sodium sulphacetamide ointment (6%) is instilled three times daily. These procedures usually ensure a relatively clear fornix and tarsal conjunctiva within a fortnight. Some follicles and some infiltration of the fornix may still remain, but the characteristic feature of this stage is the moistness of the eye. Under continued daily painting and the application of ointment, all follicles disappear and the fornix becomes more normal. The eye rapidly becomes dry.

A dry eye, however, is not necessarily healed trachoma, though in most cases nothing need be done, for spontaneous healing will now occur. The continued use of sulphacetamide ointment is helpful in consolidating the results of treatment. Scarring is minimal with this treatment; the tarsal conjunctiva remains remarkably supple and shows a pearly tinge.

In trachomatous countries, fresh cases of trachoma without marked complications are readily controlled by the instillation of chlortetracycline ointment 1.0% twice daily on three consecutive days once a month for six months.

Apart from trachoma and the virus type of ophthalmia neonatorum already discussed, the sulphonamides and antibiotics are of little value in any of the established virus infections of the eye such as dendritic ulcer, disciform keratitis, and herpes ophthalmicus. These are all viruses of the herpes group, which are particularly resistant, and it is likely that the sulphonamides and antibiotics are effective only against the larger viruses of the rickettsia type, which have an extracellular phase of existence in addition to their normal existence as intracellular parasites. In herpes ophthalmicus, treatment of the secondary infection by local application of penicillin cream (1,000 units g.), or neomycin ointment 0.5% is of inestimable value in cutting short what would normally be a prolonged and disabling affection. It is possible that one form of epidemic keratoconjunctivitis seen in some years is also susceptible to chloramphenicol ointment 1%, but most virus conjunctivitis (characterized by watery rather than mucopurulent discharge) and keratitis are still beyond treatment.

3. "Chronic Conjunctivitis"

"Chronic conjunctivitis" presents a difficult aetiological group. Many cases are not infective but congestive, being part of a chronic congestive condition of the eye as a whole from causes including possibly chronic glaucoma and irritability from uncorrected refractive errors or from exposure to dust and fumes. Some cases are part of a diffuse follicular reaction, possibly infective in origin in some instances. Rarely, an undoubted chronic infection like tuberculosis is responsible. Not infrequently a chronic inflammatory

condition of the conjunctiva is maintained by chronic dacryocystitis and occasionally by a fungus infection of the canaliculi or a virus infection of the lid margin of the verruca type. There is therefore no treatment readily available for "chronic conjunctivitis" until adequate differential diagnosis is carried through. The persistent application of antibiotic ointments is likely to add the irritation of the drug to the existing conjunctival trouble.

4. Infected Corneal Ulcer

In no ocular condition has the changing status of the antibiotics been so striking as in the treatment of infected corneal ulcers. Ten years ago most infected corneas were rapidly and gratifyingly controlled by subconjunctival injections of penicillin. In recent years such treatment has generally given disappointing results, as the organisms often responsible for corneal infection to-day are either penicillin-resistant *Staph. aureus* or Gram-negative bacilli—in all probability, as already indicated, because prophylaxis against penicillin-sensitive organisms is highly effective.

In addition to the classical serpiginous ulcer of the cornea, with its undermined edges and hypopyon reaction, there is frequently seen to-day what has been called a proteolytic corneal ulcer, in which appearances are nearer those of a corneal abscess. Clinically these types of corneal infections are distinct, and penicillin treatment is likely to be effective against the serpiginous type, while subconjunctival injection of 0.5 g. neomycin on two or three successive days will be needed for the proteolytic type. An infected corneal ulcer is a serious disorder, and the proteolytic type inadequately treated is particularly disastrous. The management of such cases is therefore a matter of expert handling. A fuller account on this and other issues raised in this article is given elsewhere (Sorsby and Ungar, 1960).

REFERENCE

Sorsby, A., and Ungar, J. (1960). *Antibiotics and Sulphonamides in Ophthalmology*. Oxford Univ. Press., London.

MEDICAL ENZYMOLOGY

FIRST EUROPEAN CONGRESS

[FROM A SPECIAL CORRESPONDENT]

The First European Congress in Medical Enzymology was held in Milan on March 28 and 29 under the presidency of Professor LUIGI VILLA. The congress was attended by well over two hundred participants from the countries of Western Europe, representation from Germany and Italy being particularly strong. In his opening speech, Professor VILLA pointed out that the extensive information from enzyme investigations in the clinical field had reached a stage where some synthesis and assessment of results was essential if further progress was to be made.

Enzyme Specificity

T. BÜCHER (Marburg) emphasized the similarity between the assessment of the meaning of patterns of serum enzymes and that of the cytological patterns of classical histology. He illustrated this point by his investigations of the locust. The various tissues of this species show remarkable specificity of enzyme pattern, especially in those of the muscles of flight as opposed to those of the muscles for jumping. The high respiratory rate of the flight muscles could be correlated with dissociation of carbohydrate breakdown and anaerobic energy production, two mechanisms normally closely associated in other muscles. He also described the close correlation between the histological development and the acquisition of enzymes by flight muscles during the five successive moultings.

B. HESS (Heidelberg) described his work on the heterogeneity of lactic dehydrogenase, as shown by electrophoresis and by chromatography on treated cellulose. The physical constants of the enzymes prepared from various tissues were different, and suggested that enzymes might be organ- or tissue-specific. He considered that, until this specificity has been more widely investigated, results of clinical enzymology must be interpreted on an empirical basis, a view also strongly supported by C. H. GRAY (London), who discussed the difficulties of interpretation in relation to the problems of correlating enzyme activity with enzyme concentration; errors due to instrumental inaccuracies and to inadequate extraction from tissues were also described.

Pregnancy Changes in Leucocytes

A. VANNOTTI (Lausanne) had extended earlier cytochemical observations of different enzymes in the various leucocytes. He had made microchemical determinations of the enzymes in cell populations containing various proportions of the different kinds of leucocyte, and by mathematical analysis derived the amounts of enzymes in the polymorphs, lymphocytes, monocytes, or eosinophils. Proteolytic activity was much greater in the polymorphs than in the lymphocytes; on the other hand, the monocytes possessed higher glycolytic and proteolytic activity, respiration, reducing power, and esterase activity than the polymorphs. Striking changes were observed in pregnancy, in which the leucocytes showed a great increase in alkaline phosphatase activity with a decrease in aerobic and anaerobic glycolysis. Similar but less marked changes occurred during the menstrual cycle, and Vannotti thought they might result from hormonal action, but such changes were also observed in tuberculosis. Very young cells of the myeloid and lymphoid series could synthesize porphyrins, but, on maturation, the synthesis stopped at the porphobilinogen stage.

G. W. LOEHR (Marburg) had investigated the enzyme content of the platelets in thrombasthenia, a disease in which there is a failure of clot retraction; he found a deficiency of some enzymes of adenosine triphosphate and perhaps of magnesium ions, all of which seem to be necessary for the contraction of a contractile protein isolated from the platelets.

Enzyme Patterns in Liver Disease

E. and F. W. SCHMIDT (Cassel) had studied a large number of enzymes in the serum of a variety of diseases of the liver, and attempted to relate their results with Bücher's hypothesis that the irregular distribution of enzymes in the subcellular particles of the liver was responsible for the "deformation" of the pattern of enzymes during their passage from the damaged cell into the blood-stream and extracellular fluid. M. J. H. SMITH (London) considered that the enzyme pattern in liver disease is of little diagnostic value, and thought that the results must be essentially empirical; on the other hand, repeated estimations would be very valuable in following the progress of hepatic disease. However, L. DEMEULENAERE (Ghent) thought that transaminase estimations were of great diagnostic value, although admitting that normal values did not exclude hepatitis. F. DE RITIS (Naples) agreed that there was abnormality of serum enzymes during acute hepatitis, but thought that the change was not necessarily an expression of necrotic hepatic lesions.

Defective Erythropoiesis

N. DIOGUARDI (Milan) had made a very complete study of numerous enzyme activities, as well as adenylnucleotides and lactic and α-keto acids, in the red cells and plasma in various disturbances of erythropoiesis. He called changes limited to a single enzyme or to several enzymes of the same chain "elective lesions" as opposed to "general lesions," in which there were changes in the enzymes concerned with a variety of metabolic pathways. Examples of elective lesions were the enzyme deficiencies of acatalasaemia.

galactosaemia (galactose-uridyl phosphate transferase), nocturnal paroxysmal haemoglobinaemia (acetylcholinesterase), and congenital porphyria (porphobilinogen isomerase). Primaquine sensitivity and favism were other examples and were usually, but not always, related to a deficiency of glucose 6-phosphate dehydrogenase, but this could not be the causal mechanism. A similar enzyme deficiency had been found in a single subject with jaundice, who, however, also showed other enzyme changes and who seemed to show an acquired type of "selective metabolic block of a complete chain." This disturbance might have been due to the toxic action of bilirubin, since it cleared up with the disappearance of the jaundice. Deficiencies of glycolytic enzymes and of adenosine triphosphatases were observed in aplastic anaemia, and high values were often found in many forms of anaemia where aplasia was not present. There was no relation between the enzymological findings and the erythrocyte count, except for malic dehydrogenase (M.D.H.), phosphoglucomutase, and glucose 6-phosphate dehydrogenase. M.D.H. was linked with microsomal residues in the red cell and seemed to be related to immaturity of the erythrocyte. These changes could therefore be related to the proportions of immature red cells present.

The serum enzymes usually paralleled the erythrocyte enzymes, especially when there was haemolysis, but the correlation was not complete, since the serum often contained enzymes which were absent from the erythrocyte. In general, however, haematological data did not correlate well with enzyme activities, and the evidence suggested that other tissues than the blood cells must play some part. Although anaemias secondary to liver damage gave characteristically high levels of enzymes in the red cells, enzyme patterns could not be correlated with the severity of the anaemia or of the hepatic damage.

Primaquine Sensitivity

H. D. WALLER (Marburg) had concentrated on the mechanism of haemolysis in primaquine sensitivity. The reduction in glutathione content and its instability on incubating the red cells with acetylphenylhydrazine was associated with higher proportions of the oxidized form of D.P.N. and T.P.N. secondary to the deficiency of glucose 6-phosphate dehydrogenase. The relative deficiencies of reduced D.P.N. and T.P.N. lead to disturbances in the glycolytic mechanism. Primaquine exaggerates these changes, which are already present in some degree in the abnormal red cells, but some other mechanism, perhaps an antigen–antibody reaction, may play a part, especially in the rapid changes which occur after exposure to the pollen of the bean (*Vicia faba*).

Fructosuria

F. LEUTHARDT (Zurich) discussed the harmless essential fructosuria and the much more serious hereditary fructose intolerance. The former was believed to be a deficiency of fructokinase, leading to an accumulation of fructose, which is harmless; the latter could be due to a deficiency of phosphofructo-aldolase, leading to an accumulation of fructose-1-phosphate which might inhibit other enzyme mechanisms and produce serious metabolic abnormalities analogous to those produced by galactose phosphate in galactosaemia. W. LAMPRECHT (Munich) described a new enzyme mechanism for the metabolism of fructose by diabetic liver, while H. AEBI (Berne) discussed the role of liver catalase in human subjects and experimental animals, especially in relation to the metabolism of C_1 units by measuring the decomposition of hydrogen peroxide and rates of oxidation of ^{14}C-labelled methanol or formate. No relationship was found between blood and liver catalase in a number of species examined. Hepatic catalase was lowered in patients with tumours.

Muscular Dystrophy

G. SHAPIRA (Paris) reported an increase in the activities of aldolase, phosphohexo-isomerase, transaminase, lactic dehydrogenase, and creatine-kinase in the serum of patients with muscular dystrophy. The change in this last enzyme was believed to be specific for the myopathies, while the estimation of aldolase was considered to have prognostic significance. Arteriovenous differences suggested that the enzymes were derived from the diseased muscles, but whether this was due to a change in muscle-cell permeability could not be demonstrated.

At the end of the congress, your correspondent was firmly of the opinion that the volume of work carried out in this field had far exceeded the ability of many workers to interpret their results. There was clearly a need for much fundamental work to be done before a satisfactory synthesis of the body of existing knowledge in clinical enzymology could be attained.

HORMONAL EXOPHTHALMOS

The Ophthalmological Society of the United Kingdom held its 80th annual congress at the Royal Society of Medicine from March 31 to April 2, under the presidency of Mr. R. C. DAVENPORT. Over 300 members and their guests attended, including a number of distinguished foreign visitors. One of the subjects debated was the "Management of Hormonal Exophthalmos."

Dr. JOHN LISTER opened this symposium. The classical triad of thyrotoxicosis, goitre, and exophthalmos gave an inadequate picture of the very varied symptomatology of this condition, he said, and the great number of possible labels for it bore witness to its complexity. His own preference was for the title "hyperophthalmopathic Graves's disease." The precise aetiology and pathological physiology remained obscure and treatment was correspondingly unsatisfactory. The first step in the management of hormonal exophthalmos was the regulation of thyroid function; if there was overactivity of the thyroid, antithyroid therapy should be used, but this had the risk of enhancing the exophthalmos. For this reason reversible measures (antithyroid drugs) were preferable to an irrevocable thyroidectomy if the danger signs of lid swelling, chemosis, or ophthalmoplegia were in any way apparent. In euthyroid cases, the anterior pituitary could be depressed by giving thyroid hormones, oestrogens, or steroids, or by irradiation of the pituitary. In hypothyroid cases, thyroid extract should always be given. If intra-orbital tension became dangerously high, diuretics could be given, but these had been of little benefit and surgical decompression might be necessary.

Mr. H. B. STALLARD discussed the surgical measures that might be needed to relieve a more severe exophthalmos. A timely tarsorrhaphy, aided if necessary by an orbital fasciotomy and division of the lateral canthal ligament, might be most important in protecting the cornea. Where a tarsorrhaphy was impossible or had failed, a large hood-shaped conjunctival flap might yet save the cornea. Orbital decompression (by orbital fasciotomy and excision of herniating oedematous orbital fat or by a lateral orbitotomy) was necessary if the optic nerve became too stretched or developed papilloedema.

Mr. MURRAY A. FALCONER pointed out that the disease was usually self-limiting so that a natural remission had often given spurious credit to each of the various forms of therapy. When corneal ulceration was imminent, he preferred a Naffziger decompression; and, even if the exophthalmos progressed post-operatively, the orbital contents could be more easily displaced backwards so that a tarsorrhaphy had then greater chances of success. Occasionally these patients died from a myocardial infarction which appeared to have some relationship, as yet unexplained, to the hormonal exophthalmos.

Mr. T. KEITH LYLE discussed the surgical treatment of the complicating diplopia. Monocular cases were easily misdiagnosed. Three out of his 32 cases had been labelled intra-orbital tumour, and two of them had been explored surgically before the correct diagnosis was reached.

Operation on the extra-ocular muscles to correct the secondary squint should be deferred until the condition was static; in his cases an average of four years had elapsed before operation. The actual operations followed the usual pattern, but it was possible to operate on the contralateral antagonist or synergist only if the limitation of movement was mild, otherwise the muscles of the more ophthalmoplegic eye would have to be resected or recessed; and it was most important to avoid any residual limitation in adduction or depression. Mr. Lyle also described a number of his cases which had shown a very inconstant visual field loss, presumably due to pressure on, or oedematous infiltration of, the optic nerve and sometimes associated with the papilloedema. They recovered spontaneously.

There was also a symposium on "The Problem of the Visually Defective Infant" in which the principal speakers were Mr. F. A. LAW and Dr. R. C. MAC KEITH. The meeting was completed by a number of short papers and two films.

Nova et Vetera

THOMAS BEDDOES, M.D., 1760–1808

In society, as in a machine, the eccentrics, though vital, are often overlooked. Born two hundred years ago, on April 13, 1760, at Shiffnall, in Shropshire, Thomas Beddoes was such a one. His birthplace itself was a cradle of industrial innovation, and throughout his life Beddoes was to derive constant stimulus from the exploitation of Nature's pantry and the unravelling of her secrets. From school he went to Oxford, where, in the intervals of satiating a passion for whist, he learned French, German, and Italian. These languages facilitated not only his medical education at London and Edinburgh, but his career as a writer, for at the age of 24 he translated Lazaro Spallanzani's *Dissertations on Natural Philosophy*. It reached a second edition in 1790 after he had also translated the physical and chemical essays of Bergman (1784–5) and of Scheele (1786). Even more exciting was his resurrection of the work of that neglected West Country chemist of a previous century, John Mayow, forerunner of Lavoisier in the discovery of oxygen.

During his years of medical training he was much influenced by Joseph Black, professor of chemistry at Edinburgh. Returning to Oxford in 1788, Beddoes became a reader in the subject, and his lectures, so his later associate and biographer J. E. Stock tells us, attracted a greater audience for chemistry than had before been known. Here he was assisted by that well-known aeronaut, John Sadler. The connexion between balloons and chemistry was close at that time. The lifting power of hydrogen, trapped in a glazed envelope, had been suggested, according to A. and N. Clow (*The Chemical Revolution*, 1952, pp. 152–4), by Joseph Black himself.

If as a chemist he was influenced by Dr. Black, as a doctor he was inspired by Dr. John Brown. To Brown's teaching that life was maintained by continuous stimuli, Beddoes applied his knowledge of the gases (pneumatic chemistry). The result of this was an institution for the treatment of the sick by "factitious airs" like hydrogen, oxygen, and carbon dioxide. Indeed, his *Considerations on the Medicinal Use and on the Production of Factitious Airs*, Parts 1 and 2, published in 1794, was followed by his edition of Brown's *Elements of Medicine, with a Preface and Notes*, and his *Outline of a Plan for Determining the Medicinal Powers of Factitious Airs* in the following year. This outline was later filled in by *Suggestions Towards Setting on Foot the Projected Establishment for Pneumatic Medicine* (1797).

Some of the time between the conception and the creation of this Pneumatic Institute at Clifton, near Bristol, Beddoes spent in raising money and equipment for it, but most of it he devoted to active pamphleteering against the restrictions imposed on the expression of political opinions by William Pitt. It was wartime; the enemy, France, was by no means unpopular with many of his friends and fellow-scientists, some of whom, like Joseph Priestley, chose to emigrate to America rather than submit to such indignities. Instead of emigrating, Beddoes hit out. A *Word in Defence of the Bill of Rights against Gagging-Bills* (1795), *Where Would be the Harm of a Speedy Peace?* (1795), *An Essay on the Public Merits of Mr. Pitt* (1796), and *A Letter to Mr. Pitt on the Scarcity* (1796) did nothing to enhance the popularity of this squat, tubby little radical among the authorities of Bristol, whom he also bombarded with *A Suggestion towards an Essential Improvement in the Bristol Infirmary* (1798).

With gas-producing machines supplied by James Watt, of Birmingham, £1,000 from Josiah Wedgwood, of Etruria, and technical assistance from James Sadler, the aeronaut, the Pneumatic Institute opened its doors. Viewed at this length of time, one can see from the numerous communications which Beddoes addressed to *Medical Facts and Observations*, the *Monthly Magazine*, the *Medical and Physical Journal*, and *Nicholson's Journal* that, by exposing hypochondriacs, opium addicts, the scrofulous, asthmatics, and the catarrhal to his "factitious airs" he was certainly applying the chemistry of his day to treat the complaints of his day.

But the Pneumatic Institute at Clifton might quite undeservedly have been forgotten had not Gregory Watt, then employed as a representative of the firm of Boulton and Watt in Cornwall, recommended to Beddoes the son of a lady with whom he was lodging. When, to Watt's recommendation was added that of Beddoes's friend Davies Giddy (later Sir Davies Gilbert, P.R.S.), the young man was taken on as an assistant. This young man showed his worth by an essay in Beddoes's *Contributions to Medical and Physical Knowledge from the West of England* (1799). His name was Humphry Davy (1778–1829). It was at the Pneumatic Institute that in 1799 Davy discovered the properties of nitrous oxide. Davy also got to know James Keir, F.R.S., who had originally wanted Beddoes to work with him. Davy also met Beddoes's own father-in-law, Richard Lovell Edgeworth.

It was Edgeworth who acknowledged Beddoes's contributions in another field: that of educational theory. Edgeworth and his daughter Maria were intensely interested in what is now regarded as progressive education: placing the child in a position where it can find out things, and the relationships between things, for itself. In their book, *Practical Education* (1798), the Edgeworths acknowledged Beddoes's help in the chapter on toys. For Beddoes had for some time previously been engaged in trying to promote the manufacture of what he called "rational toys," models which could be taken to pieces and so become the instruments whereby information and knowledge about the principles of "mechanics, chemistry, and technology" could be acquired and the senses improved. Nor did this exhaust Beddoes's educational enthusiasms. As early as 1792 he had printed, but not published, *A Letter to a Lady on the Subject of Early Instruction, Particularly that of the Poor*, following it up two years later by *A Guide for Self-Preservation and Parental Affection*, and in 1801–2 with a series of papers entitled *Hygëia*; or *Essays, Moral and Medical, on the Causes Affecting the Personal State of the Middling and Affluent Classes*. And Beddoes practised what he preached. He was practically a total abstainer, he refrained from "copious draughts" of tea, and he walked wherever possible upon the business of his profession.

Beddoes was anxious to improve medical education, too. From 1803 onwards his activities were outlined in a paper entitled *Instruction for People of all Capacities Respecting their own Health and that of their Children*. He began to give medical lectures, and was joined by Dr. J. E. Stock, who later wrote his biography, in vaccinating the local inhabitants. At a very early stage in his career he had advocated dispensaries for the sick poor, and now the "sick and drooping poor" were to be cared for in his institution

(*Continued at foot of next page*)

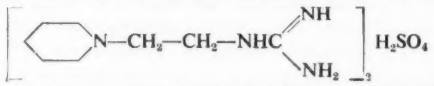
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Guanethidine

"Ismelin" (Ciba).

Chemistry.—This is N-(2-perhydroazocin-1'-yl-ethyl)-guanidine sulphate and has the following structural formula:



Pharmacology.—Guanethidine interferes with the release and/or distribution of transmitter substances from the sympathetic nerve terminals. In animal experiments its actions can be divided into acute and chronic phases, but the acute, transient blocking effect on sympathetic ganglia is unimportant in connexion with its therapeutic use as a hypotensive agent. In the chronic phase its action is characterized by sympathetic atony. This is due, not to ganglionic blockade, nor to interference with transmission along pre- or post-ganglionic fibres, but probably to interference with the release of transmitter substance between the nerve ending and the adrenergic motor end-organ. As a result of this chronic sympathetic atony, it exerts a prolonged hypotensive effect.

In animal experiments it has been shown often to potentiate the effects of noradrenaline and vasopressin, while reducing or abolishing the pressor effects of amphetamine and ephedrine. Unlike ganglion-blocking drugs, guanethidine does not reduce the pressor response to splanchnic-nerve stimulation. In its chronic phase of action no interference with the parasympathetic efferent flow has been observed.

Therapy.—It is advocated for the control of hypertension. Tolerance has not so far been noted from continuous treatment. Like bretylium (February 13, p. 496) guanethidine offers the possibility of selective attack on the sympathetic nervous system without interference with the parasympathetic, though the two drugs are chemically unrelated and their precise mode of action is different.

Guanethidine may be given in a single test dose initially of about 30 mg., before starting daily treatment with doses of 10 mg., which may then be gradually increased by increments of about 10 mg. at weekly intervals, until the desired reduction in blood pressure is attained. Most patients require about 30 to 60 mg. guanethidine daily, but individual variation is fairly large. The full effect of the drug is not seen for several days, and its effect persists for four days after withdrawal.

Side-effects.—Postural hypotension can be troublesome, and for this reason the dosage of the drug should be increased cautiously and by stages. Diarrhoea is the other most frequently observed side-effect. No serious toxic effects have so far been reported.

N.H.S. Basic Price.—100 10-mg. tabs. for 40s. 5d.; 100 25-mg. tabs. for 95s. 5d.

(*Continued from preceding page*)

on payment of half a crown. He urged the farm labourers of his day to refrain from the eating and drinking marathons with which they used to celebrate harvest home.

But his admonitory voice and pen could not go on for ever, and he died on Christmas Eve, 1808, leaving his son, Thomas Lovell Beddoes, then aged 5, in the care of Davies Giddy. Samuel Taylor Coleridge remarked of his departure that "more has been taken out of my life by this than any other event." Coleridge should have known. He was himself a victim of the opium habit, one of the very scourges which, with scrofula, phthisis, and catarrh, the Pneumatic Institute had been founded to eliminate.

W. H. G. ARMYTAGE.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Undescended Testicle

SIR,—There is still much confusion of thought on this subject, particularly at two points. The valuable survey of schoolboys by Drs. Barbara Ward and W. M. Hunter (April 9, p. 1110) confirms once again that, if left alone, the majority of testicles absent from the scrotum will "naturally descend into the scrotum at puberty." But what is this so-called natural or spontaneous descent at puberty? Is it, as is generally implied, a process of true migration of the organ similar to that which occurs normally between the seventh and eighth months of intrauterine life? Or is it accounted for by the relaxation of an overactive cremaster muscle? The evidence in favour of the former hypothesis is incomplete and unconvincing.

The answer to the problem may ultimately be found in what occurs before the age of 5. Very few investigations of the position of the testicles in infants and *young* boys have been made, and in consequence we are largely ignorant of the natural history of testicular descent and of the cremasteric reflex. In my own brief observations the cremaster has been found to be almost completely inactive at birth and during the first few months of life. Stimulation of the skin on the inner side of the thigh will usually cause a slight, momentary lift of the testicle, but will not make it jump to the upper part of the scrotum or the groin, nor keep it up there. Apparently strong cremasteric activity is a phenomenon of boyhood. Moreover, although the overall incidence of undescended testicle at birth was 3.4% in 1,500 full-term boys at birth (the testicle being 4.0 cm. or less below the pubic crest), by the age of 12 months the incidence had fallen to 0.7%.[1,2] A second (unpublished) series of 1,000 infants has shown a similar low incidence a few months after birth. If these observations are true, it suggests that contraction of the cremaster may be the whole explanation of the relatively high incidence of "undescended testicles" in boyhood and relaxation the reason for its "descent" at puberty. It is time this problem was solved.

Figures, as we know too well, may sometimes be misleading. Unfortunately, collected series of schoolboys (and of adults) with undescended testicles almost always lose their value because we have not yet agreed as to how we should define an undescended testicle. If, for instance, it can be coaxed over the pubic bone into the upper part of the scrotum but no further, is it counted as descended or undescended? If we agreed to measure descent from a fixed point (say, the upper border of the pubic bone), we would then understand each other better. Such a method of measurement may be approximate only, but it can be done in a moment and it forms a useful index for assessment at future examinations, especially if carried out by another doctor.—I am, etc.,

Hillingdon Hospital, Uxbridge. C. G. SCORER.

REFERENCES

1 Scorer, C. G., *Arch. Dis. Childh.*, 1956, **31**, 198.
2 —— *Brit. J. Urol.*, 1955, **27**, 374.

SIR,—Evidence is once more offered by Drs. Barbara Ward and W. M. Hunter (April 9, p. 1110) of the widespread inability to distinguish the genuine undescended testicle from the commoner and perfectly normal retractile one. In a leading article in the same issue (p. 1118) you rightly incriminate "the doctor with cold hands" as "the commonest cause of undescended testicle." But when your leader-writer adds "for the contracted cremaster muscle of a child often holds the testis out of the scrotum for a long time, thus simulating cryptorchism, so that the diagnosis of undescended testicle (cryptorchid as distinct from ectopic testicle) is apt to be very difficult and time-consuming," he fails to recognize the undoubted fact that the contraction of cremaster can easily be overcome and so paints too gloomy a picture of the situation. The purpose of this letter is to attempt to dispel this gloom by showing that it is always possible to demonstrate the retractile testicle for what it is by means of a manœuvre so simple that it should not need to be described here but which evidently is seldom used by practitioners examining children.

The retractile testis can be manipulated to the bottom of the scrotum without undue traction. If this cannot be done after repeated attempts, the testis is abnormal. The patient is best examined supine on a couch with the legs slightly separated. Relaxation is helpful but not essential. Handling the immature testis does not cause discomfort, but excessive ticklishness may be troublesome. If the retracted testis is visible or palpable it must be in the superficial inguinal pouch, and from this position it simply requires to be massaged down to the neck of the scrotum, where it can be grasped between finger and thumb through the thin scrotal tissues and drawn slowly down to the bottom of the scrotum. The power of cremaster is not great and it can be felt to give as the testis is pulled down. The cord may then be palpated with the free hand and is felt to be slack in contrast to that of the testis undescended because of a short cord.

Often in young boys the testis retracts into the inguinal canal, where it becomes invisible and impalpable. This is the situation which most often deceives the uninitiated. It is always possible, however, to massage the testis out of the external ring, when it can be grasped and brought down as above. The most effective method of massage is to place the fingers of the left hand flat on the abdomen lateral to the internal ring, and, exerting firm pressure, slide it slowly down and medially towards the external ring. The right hand is held in readiness to grasp the testis as it emerges into the superficial inguinal pouch. If the testis does not appear the manœuvre is repeated several times before deciding that the testis is not retractile. To enable the fingers to slide easily it is often helpful to dust the skin lightly with talcum powder.

This simple technique will separate the normal from the abnormal testicle, which is all that most doctors are required to do.—I am, etc.,

Westminster Children's Hospital, London, S.W.1. D. M. FORREST.

SIR,—I am surprised that Mr. Denis Browne did not rise in his wrath to smite your leading article of April 9 (p. 1118) hip and thigh. The communication of Drs. Barbara Ward and W. M. Hunter (p. 1110) gives confirmation to the accepted low incidence of undescended testis. A leading article in the *B.M.J.* should give up-to-date information, and it is sad that such out-of-date advice should be given.

I would be very grateful to learn how the author of your leading article can make an early diagnosis of *proved* cryptorchidism. Undoubtedly he will obtain good results by the early treatment of cryptorchidism by gonadotrophins. Many of us obtained such results 20 years ago—usually in patients where testes would have descended spontaneously in due course. Early surgical treatment of "undescended testis" will be successful in "undecided testis." Imperfect development of the testis interferes with descent; it is not, as your leading article suggests, that imperfect descent interferes with development.

The statistical evidence that there is a vastly greater risk of malignant change in an undescended testis does not bear intelligent analysis.—I am, etc.,

Royal Hospital for Sick Children, Glasgow, C.3. W. M. DENNISON.

SIR,—There is a leading article on this subject in your issue of April 9 (p. 1118) which refers to an article by Drs. Barbara Ward and W. M. Hunter entitled "The Absent Testicle" in the same issue (p. 1110). Your leading article will be read by many who do not refer to the article in detail, and, as it is in part misleading, I feel you should correct it.

"If the testes do not descend *before birth* it is usual, even in normal testes, for no further descent to take place until puberty." (My italics.) The only reliable surveys of undescended testicles *at birth* are those of Scorer,[1 2] who showed that most testes undescended at birth come down within the next three months. He showed that descent after this age is uncommon. You go on to say that the paper by Drs. Barbara Ward and W. M. Hunter gives "further valuable statistical evidence of this phenomenon." The phenomenon is descent at puberty. The evidence submitted in this paper is inadmissible on statistical grounds.

(1) It is bedevilled, as is the whole subject of undescended testicles, by observer error. This is admitted in the article, only it is called "variation in observers."

(2) "Absent testicles" occurred in 0.41% of post-pubertal boys in 1957 and 0.23% in 1958. This variable approaches 100%. Again the obvious error called "experience gained by the observers" invalidates the 1957 figures. Perhaps a survey for 1959 would invalidate the 1958 figures.

(3) The percentage of undescended testicles in the 1958 series actually *rose* as the children got older. It was 1.15% at 5 years, 2.40% at 8, 4.05% at 11. Is there any better explanation for this than "this possibility that retraction may occur more readily in boys of 7–11 years than in 5-year-olds"? This is an admission that retractile testes are included in the pre-pubertal group of "testicle absent." The incidence of undescended testicles revolves around the subject of the retractile testis. Any series which includes retractile testes as "absent" is of no real statistical value.

(4) "It was difficult to determine by one examination alone whether an apparently undescended testicle was actually undescended or merely retractile." I couldn't agree more. There were 198 patients in the 1958 "absent testicle" group. How many times were these examined?

(5) The low figure (0.23%) given as the post-pubertal incidence in the 1958 series excludes "boys who received any form of treatment." How many boys did it exclude? Most treatment of this condition takes place between the ages of 5 and 14 years, but the present survey, if continued longitudinally, would include those with genuine undescended testicles to begin with but would exclude them later when they, quite properly, began treatment before puberty. The final figure is a false low one.

Sir, this is not "valuable"; this is not statistically sound and therefore no "evidence." As a paediatric surgeon may I say that school medical examinations are

valuable and important, and that examination for undescended testicles is an integral part of them.—I am, etc.,

Dublin. BARRY O'DONNELL.

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[1] Scorer, C. G., *Brit. J. Urol.*, 1955, **27**, 374.
[2] —— *Arch. Dis. Childh.*, 1956, **31**, 198.

Ischaemia in Limb Injuries

SIR,—I was interested to read the article on acute ischaemia in limb injuries (April 2, p. 1001). No one could quarrel with the conclusions of Mr. E. G. Hardy and Mr. D. J. Tibbs that treatment must be urgent, that soft-tissue trauma often renders failure inevitable, and that firm and pulseless injured arterial segments are frequently thrombosed or occluded. One wonders, however, what induced them to carry out arterial reconstructions on limbs that were ischaemic for periods of 12 to 28 hours. They say they are disappointed at six failures out of nine cases under such conditions. Why? What did they expect? As they rightly point out, skeletal muscle is very sensitive to ischaemic conditions. This is due to its high metabolic activity and its high degree of specialization, lessons that we learnt in the physiology department. What did they think reconstructive arterial surgery would achieve after such long periods of deprivation of blood? The pathology is parallel with that of frostbite or trench-foot. Must we learn all over again that to thaw out rapidly such cases means moist gangrene, toxic absorption, and finally amputation? It would surely have been wiser to assist Nature's method of dealing with the problem—i.e., to persevere with a collateral circulation and to try to improve this gradually. The precise method to use would depend on the individual case. In this way one or two limbs might well have been salvaged.

I would also take issue with Mr. Hardy and Mr. Tibbs on the question of arterial spasm. This is a definite entity, and those who taught it in the past knew what they were talking about. There is no doubt that a vessel of the calibre of the superficial femoral can contract down to the size of the lead in a pencil, that the anterior or posterior tibial can become as narrow as a piece of cotton thread. I have seen it happen. Spasm, especially spasm of collateral vessels, is an important feature in *acute* ischaemia. As Sir George Pickering has pointed out, the important fact to remember is that arterial spasm is always associated with an organic cause.

Finally, let it be remembered that authoritative writings are authoritative.—I am, etc.,

Middlesbrough. S. MOTTERSHEAD.

Conservative Treatment of Ulcerative Colitis

SIR,—The recent letters on the conservative treatment of ulcerative colitis (March 19, p. 876; April 9, p. 1130) have prompted us to report a few observations on the association of carcinoma and ulcerative colitis as seen at this hospital.

We agree with previous reports that the prognosis of carcinoma complicating ulcerative colitis is poor, although our figures are a little better than others so far reported; 6 of our 19 patients survived five years (31.6%). It is interesting that in a high proportion of our patients (8 out of 19) the site of the tumour was in the rectum.

With regard to the assertion that the disease in the remaining rectum after ileo-proctostomy will resolve once the whole of the ulcerated colon has been excised, we wish to point out that in all the surgical specimens of ulcerative colitis examined at this hospital which also contained a carcinoma the intestinal mucosa showed little gross evidence of ulceration and had the histological appearances of a healed ulcerative colitis with only slight residual inflammation. We feel that it is relevant to this discussion that carcinoma in ulcerative colitis develops from mucous membrane which often shows no sign of active disease and histologically is healed or at least in a quiescent phase.—We are, etc.,

B. C. MORSON.
H. E. LOCKHART-MUMMERY.
W. F. W. SOUTHWOOD.

St. Mark's Hospital, London, E.C.1.

Dangers of Halothane

SIR,—I would like Dr. H. Rex Marrett (April 16, p. 1208) to explain how, if halothane is given as Drs. C. Langton Hewer and R. I. Ballantine gave it (March 19, p. 876), "should there be any respiratory depression, the blood concentration will continue to rise." In these circumstances the alveolar concentration of halothane vapour cannot be more, and in practice will always be less, than the percentage setting of the vaporizer, and it will decrease as the dead space becomes a larger proportion of the tidal volume.

Dr. Marrett is postulating a rising concentration of halothane in the blood associated with a diminishing partial pressure of its vapour in the alveoli. Is he not trying to make water flow uphill?—I am, etc.,

Southampton General Hospital, Southampton. P. J. HORSEY.

Intelligence and Prematurity

SIR,—Your annotation (April 2, p. 1036), which comments on the latest paper from the national follow-up survey of premature and maturely born children,[1] raises an important methodological question, pertinent not only to this study but to socio-medical investigations in general. The use of "paired" controls, which is legitimate in therapeutic trials or biological assay where one specific question needs to be answered and where subjects are allotted at random to the experimental and control groups, is totally inapplicable in the type of investigation here described.

One presumes that in planning this study the authors were concerned to detect what differences in physical and mental development, if any, could be attributed to premature birth *per se*, the assumption being made that the complex and varied biological and social factors affecting a child's subsequent development could be adequately eliminated by "matching" for sex, birth rank, Registrar-General's occupational classification of father, age of mother, degree of overcrowding, and locality. On this basis Douglas states in a recent book,[2] "the homes were in every way similar."

This kind of assumption can result in quite misleading conclusions being drawn—for example, differences found in weight and height measurements at 4 years[3] which were associated with differences in maternal height (this being an unmatched factor) were assumed to be largely genetic in origin. The theory that the smaller stature of some mothers of prematures might be due to unfavourable influences in their own childhood was dismissed, because control and premature groups were closely matched, and differences between mothers were just as large in different social groups. It now transpires that other factors, hitherto unrecognized, *were* of importance—in particular, the social and educational background of the parents. A similar finding was previously reported by me[4] when it was shown that if a premature baby

having a father in social class 3 was matched with a mature baby with a father of like social class the premature would have a 60% chance, and the control baby only a 37% chance, of having a mother brought up in a lower social grade.

As your annotator suggests, the most satisfactory way of selecting the necessary control group would be to choose a random sample of maturely born children from the same general population, as has been done in the current Edinburgh investigation of later development of children of varying birth-weight.[5] One should guard against deciding beforehand what factors in environment and upbringing are most important, and endeavour to observe and record as objectively and quantitatively as possible any facets of the environment which may or may not have a bearing on later development, and allow the data to speak for themselves. This cannot be done by depending on the subjective assessment of a large number of voluntary observers working in isolation, but only by a close personal observation, preferably within the home, by one worker, or a small number working in close co-operation. Large-scale national investigators can produce useful results about broad, well-defined, and easily measurable types of data, and are profitable in indicating further lines of more intensive study, but are of little value in assessing the effect of different patterns of child care and social background on as complicated a subject as child development.

With regard to the mental development of prematures in the national survey, radically different conclusions have been drawn from the three age-groups studied: (1) In the pre-school period prematures were not considered to be retarded, if allowance was made for degree of prematurity, this conclusion being based on the report obtained by the health visitor when the child was 2 years old about the alleged age of walking.[6] (2) At 8 years small handicaps were found in the premature group on tests of reading, vocabulary, and intelligence, as well as a small increase in gross handicap, but a possible environmental explanation was thought unlikely. (3) At the age of 11-plus a marked difference was found between prematures and matures in the grammar-school promotion examination. Now it is thought that these differences are largely explained by poor living conditions, low standards of care, and lack of parental interest, all of which were apparently not noticeable three years previously. It is fortunate that a concurrent investigation has brought to light certain differences in the social milieu of the two groups, but it is not a simple matter to go back over eleven years and unearth data which might have been recorded from the beginning if the fallacy that it is possible to match the "unmatchable" had been avoided.—I am, etc.,

Department of Child Life and Health, University of Edinburgh. C. M. DRILLIEN.

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3 —— Mogford, C., and Blomfield, J. M., *Arch. Dis. Childh.*, 1953, **28**, 436.
4 Drillien, C. M., *J. Obstet. Gynaec. Brit. Emp.*, 1957, **64**, 161.
5 —— *Arch. Dis. Childh.*, 1958, **33**, 417.
6 Douglas, J. W. B., *Med. Offr*, 1956, **95**, 33.

Inoculation Technique

SIR,—In your issue of April 9 (p. 1133) Dr. G. M. Ingall writes, "In the Royal Navy I immunized thousands of individuals, using a 20-ml. syringe and changing the needle. I have never read of, or can imagine, any way that this could be dangerous." If Dr. Ingall is not pulling our legs about the depth of his professional ignorance, I should advise him to read any current modern textbook of medicine on the subject of homologous serum hepatitis—and the sooner the better. If he would like his imagination stirred by something relevant to the Royal Navy, he might look up the reference to the work of Ellis,[1] which showed that there was a disproportionately high incidence of jaundice among those who had recently received typhoid-paratyphoid vaccine or tetanus toxoid.

Dr. Ingall rejected the use of the word malpractice, which Professor Anderson reasonably used. I wonder if Dr. Ingall would prefer to substitute "culpable ignorance." But surely he *is* pulling our legs.—I am, etc.,

Department of Bacteriology, University of Glasgow. J. W. HOWIE.

REFERENCE

1 Ellis, F. P., *J. Hyg. Camb.*, 1953, **51**, 145.

SIR,—I, too, feel that Professor Thomas Anderson's letter (March 19, p. 882) cannot pass without comment. As a National Service man I spent 21 months as medical officer to a Primary Training Centre for recruits. A new intake came in every six weeks and stayed ten weeks. In that time the recruits had two injections each of T.A.B. and tetanus toxoid, and were vaccinated. The inoculation programme started on the third day of intake and was completed in four weeks. Thus each recruit had four injections and one vaccination. I estimate that well over 1,000 recruits passed through my hands in that 21 months.

For the first six months I used the old-fashioned method of changing the needle after each injection, using a multiple-dose syringe. After that I introduced the system of sterilizing the needle, without removal from the syringe between doses, by immersing in an oil bath heated to 120° C. for three seconds. When vaccinating against smallpox I blew the lymph from the tubes. In the course of giving 4,000 injections I had one case of infectious hepatitis in the barracks—in a member of the permanent staff who had not had any injections for six months. Neither did any of my 1,000 vaccinations develop secondary infection. And as the recruits did not leave my care until six weeks after the last injection (i.e., the incubation period of infective hepatitis) I feel the follow-up period was complete. Perhaps I was lucky, but 4,000 injections . . .—I am, etc.,

Truro. DAVID HOOKER.

SIR,—I have followed with interest the correspondence on the above subject. The implications are of course very much wider. Few would dispute the principle that where the health and the safety of the patient are concerned, only the best is good enough. It is unfortunate, however, that in the sphere of general practice the best is often not attained. This is to be attributed partly to the human failings of mankind, including the G.P.'s, and partly to the system under which we have to work.

Few would doubt that, ideally, every injection should be given with a freshly sterilized syringe and needle, and the dose should be taken out of a freshly opened ampoule. Many bacteriologists would maintain that the syringes should be dry-sterilized. But it is difficult to imagine these ideal techniques being carried out under present conditions.

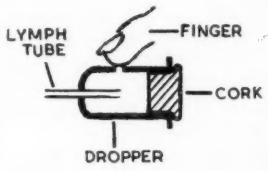
For the large amount of time and expense incurred in connexion with these programmes of mass immuniza-

tion the G.P. is paid 2s. 6d. per injection, which is later deducted from the Central Pool—in other words, no additional remuneration is, on balance, received for the work. It can only be surmised what further programmes of mass immunization the G.P. will be asked to undertake in the future, and it is high time that not only the aseptic techniques but also the remuneration be considered at a very high level. It is unrealistic to regard this service as part of the general practitioner's normal burden when it occurs on such a grand scale.—I am, etc.,

Gosport, Hants. TERENCE M. DORAN.

SIR,—The recent correspondence on smallpox vaccination prompts me to tell you of the home-made vaccine expeller which I have been using for 3–4 years.

All that is required is a rubber dropper (from an empty nose-dropper bottle) and a small cork (the ones used to plug the ends of the lymph tubes are usually all right, but a rubber one—out of a disused "viule" cartridge—is better): total cost—*nil*. To make: insert the cork into the open end of the dropper, and, with a No. 12 needle heated to red heat, make a hole in the dropper away from the cork—that is, in the rounded end—and another in the side. To use (see Fig.): simply break off the end of the lymph tube and push it in the first hole, and then break off its other end. Put your index finger over the second hole and squeeze the dropper. (The second hole is to prevent premature expulsion of the lymph when the distal end of the tube is broken off.)—I am, etc.,



Salford, 7. M. J. DERBYSHIRE.

SIR,—The correspondence (April 2, p. 1055) on methods of expelling lymph from a capillary tube makes me wonder whether it has not been generally observed that the vaccine flows fairly rapidly of its own accord down the tube if it is held vertically once both ends have been broken. If one point of fracture is made reasonably close to one end of the lymph column, say within a quarter of an inch, the time spent waiting for the vaccine to reach the open end is in nearly every case negligibly short, and when the end of the tube is touched to the skin it thenceforward flows freely to cover an economically small but sufficient area. If it chances that several vaccinations are to be made at the same session, there is no delay at all after the first, as the lymph is already presenting at the end of the tube, and there is also very little difficulty in using one tube for five or six vaccinations. Very occasionally, indeed, the lymph is reluctant to flow at first and resort has to be made to blowing, if tapping the tube does not hasten effluence.—I am, etc.,

London, N.W.1. H. DE GLANVILLE.

SIR,—May I suggest an even simpler way of expelling the lymph from the sealed tube in which it is supplied, and which I have used for many years with entire satisfaction? Break off one end only of the tube and, holding the latter with its open end over the selected position, apply a flame to the other end; the expansion of air in the closed end by the heat expels the lymph immediately. The flame can conveniently be derived from the bit of cotton-wool soaked in spirit which was used to sterilize the skin, and which then being ignited is used first to sterilize the mounted needle and then expel the lymph. Apart from the occasional need to reassure an anxious mother that one is not about to set fire to the baby, I have found no objections to this method.—I am, etc.,

St. Germans, Cornwall. W. H. SPOOR.

Diabetes in General Practice

SIR,—I read with great interest the excellent report of Dr. I. H. Redhead on the incidence of glycosuria and diabetes mellitus in a general practice (March 5, p. 695). This was read with particular relish because in the winter of 1946–7 I lived in Dr. Elliott P. Joslin's farmhouse in Oxford, Massachusetts, with 12 accomplices while undertaking with Dr. Hugh L. C. Wilkerson the original study reported in the *Journal of the American Medical Association*.[1]

We have now studied the original group for more than 12 years and feel that our original criteria, if anything, were too lax rather than too selective. We used the standard of 170 mg./100 ml. venous blood, Folin–Wu method, 1–2 hours after the largest meal of the day as a criterion for presumed diabetes. By and large, this has withstood the test of time. Of more interest is our "suspect" group (those with repeated postprandial blood-sugar values greater than 140 mg./100 ml. Folin–Wu). After 12 years, 27 out of 118 in this group have become diabetic as compared with only 4 who now have diabetes out of 225 "normals" in the control group. The prevalence of diabetes in the "slightly above normal but certainly not diabetic" category is more than 10 times greater than in those with consistently lower postprandial blood-sugar values.

As inferred in the excellent *British Medical Journal* article, one must also cast a jaundiced eye on the allegedly harmless glycosurias. Four out of our original 17 persistent unclassified glycosurias (with normal blood-sugar values) have become diabetic in the ensuing 12 years. However, true renal glycosuria is somewhat rare. Dr. Elliott P. Joslin tells me he has only 93 classified out of 55,000 cases of glycosuria with 558 as potential diabetics. He is now starting to follow up 8,250 "unclassified glycosuriacs," and these should make interesting reporting later.

In spite of the fact that postprandial blood-sugar levels are far superior to urine for general case-finding, one must adapt one's method to the opportunities at hand. Efforts like those of Dr. Redhead are to be encouraged. Since we have a poor record of the amelioration of the complications of far-advanced, untreated diabetes, perhaps it will be more fruitful to find cases much earlier and to treat them more vigorously than with generally accepted therapeutic standards to date.—I am, etc.,

Boston, Massachusetts. LEO P. KRALL.

REFERENCE

[1] Wilkerson, H. L. C., and Krall, L. P., *J. Amer. med. Ass.*, 1947, **135**, 209.

SIR,—The letter by Dr. F. I. Powell and Dr. R. E. Blair (April 2, p. 1049) points to the need for more investigation into the epidemiology of diabetes mellitus in Britain. The occurrence of localized groups of

diabetes is, I think, probably not uncommon, and there are several possible explanations of such a state of affairs.

The first is that those concerned are related to each other, the facts that they live close together and that they have diabetes each being the product of their consanguinity. The type of locality might likewise be a factor. If it is one of the poorer parts of a town or village, it may on that account contain a disproportionate number of elderly people who, because of their age, are more likely to have diabetes than are younger persons.

Another possibility is that some members of such a localized group of diabetics may have been diagnosed in the first instance by neighbours who were already known diabetics. There is a vast number of undiagnosed diabetics in Britain, and even those experiencing diabetic symptoms may not seek medical advice for prolonged periods because of ignorance of the nature of their symptoms. Should such undiagnosed diabetics come into contact with patients in whom the disease has been diagnosed the latter may well be instrumental in bringing the former to medical attention for the first time. A more remote possibility is that a family doctor, having diagnosed diabetes in one patient in a street, may suddenly be reminded that such a diagnosis would account for the symptoms of another patient living near by.

I do not suggest that any of these tentative explanations is necessarily applicable to the circumstances described by Drs. Powell and Blair. There may be other environmental factors involved, or the state of affairs may have arisen purely by chance. My plea is that more study should be devoted to the epidemiological and socio-medical aspects of diabetes mellitus.—I am, etc.,

Health Department, Northampton. J. J. A. REID.

Diabetes in the Bantu

SIR,—I appreciate that the collection and interpretation of data on the incidence of diabetes mellitus in any community is fraught with difficulty. The report by Drs. W. M. Politzer, B. Hardegger, and T. Schneider (February 27, p. 615) of an incidence of 0.23% of 3,000 Basuto cannot, however be accepted uncritically. It is essential to determine the contribution made to this figure by the age and sex structure of the population examined.

I have taken the liberty of rearranging the data in their first Table. Assuming the subjects are evenly distributed in the decades reported, I have divided them as seen in the accompanying Table. A comparison may

Ratio of Diabetics in the Population

Age-group (Years)	Female		Male	
	American	Bantu	American	Bantu
25–34	1/900	1/716	1/1100	0/154
35–44	1/300	1/158	1/500	1/156
45–54	1/125	2/280	1/225	0/137
55–64	1/50	0/178	1/100	0/86·5
65+	1/45	1/121	1/70	1/48·5

then be made with the incidence in each age-group of an American population as recorded by Joslin and Krall.[1] It will be seen that too few males were examined to permit of comparison; however, on considering the data, an unexpectedly low incidence in females over 55 years emerges; this most interesting finding would appear to be at least partly responsible for the low overall figure.

My own experience in the African,[2] admittedly in an urbanized population, is rather different. The quoted figure of 0.4% of patients admitted to Baragwanath Hospital must be qualified by the recognition that trauma to young males determines many admissions. This figure for known diabetics in a hospital population is not directly comparable to the incidence of 1.7% in Wilkerson and Krall's study[3] of most of the population of a small town. Using their figures to calculate the total number of diabetics from the number of known diabetics, the true incidence may be estimated at 0.7%. In my opinion this is a conservative estimate.—I am, etc.,

Baragwanath Hospital and University of the Witwatersrand, Johannesburg. K. J. KEELEY.

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2 Keeley, K. J., *S. Afr. med. J.*, 1957, **31**, 1284.
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Chlorpromazine in Tetanus

SIR,—We read with interest the comments of Dr. R. Wright and Professor E. B. Adams (January 30, p. 345) on our article on chlorpromazine in tetanus (November 28, p. 1150), and we hope that you will allow us to answer some of the points raised by them.

In spite of being aware of the definition of the period of onset of tetanus by Cole,[1] we believe that the period of onset of any disease (including tetanus) is the period that elapses between the onset of first symptom and the earliest time when a definite clinical picture of the disease has developed. Perhaps Dr. Wright and Professor Adams will agree that the period of onset cannot be said to be reduced to naught when the first symptom of the disease is not the generalized rigidity, and it takes some time for it to appear and reflex spasms do not occur. Fever, chilliness, abdominal pain, pain in back and neck, and many other symptoms have been described as first in tetanus. In our six mild cases the first symptoms described were pain in back, pain in neck, and difficulty in swallowing, and the period of onset denotes the time that elapsed between the onset of these symptoms and the onset of generalized rigidity.

As for the dosage used by us, we have emphasized that with paraldehyde as an adjunct we have used a smaller dosage of chlorpromazine. Even Professor Adams admits to have experienced the effectiveness of chlorpromazine only when combined with phenobarbitone in serious cases. We may point out that our purpose was not to judge the dose of chlorpromazine when used alone (which has been sufficiently studied and subsequently abandoned by Professor Adams and others), but to evaluate a therapy which may reduce the mortality rate without undue side-effects. We did not use chlorpromazine alone in high doses, we must admit, as we were discouraged by the reports of Professor Adams and Dr. Laurence,[2–4] who did not report any increase in survival rate after such a trial. Laurence *et al.*[2] reported chlorpromazine poisoning in one case in whom post-mortem examination was done (some other patients may also have died of chlorpromazine poisoning?) and evidence of muscular induration, etc., in many other cases which might have aggravated the disease. This was not our experience with a lower dose in combination with paraldehyde, and that is why we emphasized that a higher dose, whether alone or in combination, is unnecessary and hazardous. We believe that Professor Adams has himself come to a similar conclusion.

A cure rate of 92.3% as reported by us in non-neonatal cases who survived more than 24 hours should not have conveyed a false sense of effectiveness, considering the fact that we have reported a 20% overall mortality in this group and that we have ourselves admitted that the number of cases we treated was too small for any statistical analysis. Nevertheless we reported our clinical impression as we should have done. We may repeat that the mortality figures from different centres do vary, as Professor Adams agrees, and in this connexion we may refer to the letter of Dr. B. J. Vakil (January 2, p. 56), who claims 75% survival rate with a combined therapy of chlorpromazine and barbiturate in more than 340 cases from Bombay. There is a significant difference in the mortality figures of Professor Adams and Dr. Vakil. Dr. Vakil also has emphasized the fact that the lower dose of the drug reduced the incidence of complications.

Lastly we wish to stress that: (1) We were able to use a lower dose of chlorpromazine only because we used paraldehyde as an adjunct. We are not aware of any comparable series in which paraldehyde and chlorpromazine have been used in a similar dosage. (2) We did not administer more than two injections of chlorpromazine in 24 hours to avoid muscular induration which has been reported by Laurence *et al.*[2] (3) This combination of chlorpromazine with paraldehyde as an adjunct gave us very encouraging results in the small number of cases that we published. —We are, etc.,

AJAI SHANKER.
L. S. MEHROTRA.

Bhopal, India.

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Late Lactation

SIR,—One of the effects of the present "back to tribalism" policy of the contemporary South African Government is an accentuation of the problems of migratory labour. It is common for young infants to be left in the care of their grandparents while the mother returns to her work in the cities. Left thus, the infants are given a diet of gruel with, in the summer months, an addition of milk ; they are also put to the grandmother's breast. The aged nipple acts as a live dummy, soothing and serving to deepen the emotional ties which exist between the couple in the absence of a more usual mother-and-child relationship.

Tradition has it that lactation occurs, but it is in fact extremely unusual for this to happen. Recently, however, we have come across a case in which actual milk is being secreted. The woman, a Zulu born in 1906, is more than four years past the menopause. She has had nine children, fed all of them on the breast, and buried two. Her last child is now about 18 years of age. The amount of milk is not great, though it is sufficient to squirt from the nipple on expression ; it is of normal colour for human milk. We should be interested to know whether others working in the less-developed areas of the world have come across similar cases.—We are, etc.,

MARGARET BARKER.
ANTHONY BARKER.

Charles Johnson Memorial Hospital, Nqutu, Zululand.

Therapeutic Abortion

SIR,—I was interested to read the full text of Professor T. N. A. Jeffcoate's lecture to the Association (February 27, p. 581), and still more interested to read the critical letters you have published. Dr. Peter Darby's letter (March 26, p. 964) analysing the original article hits home accurately on all six points, and finishes with a glimpse of what to me is the obvious, though I doubt whether it will be accepted by my consultant colleagues, and that is that the person best suited to give an opinion on the need for abortion is the general practitioner.

My doubts regarding the consultants are based on the certainty that once a consultant has expressed his personal point of view—and he of course will be the necessary pair of hands in surgical treatment—he will only be consulted by the family doctor of the woman concerned if that doctor is sure that his patient will be treated sympathetically and kindly, and not with undue pompous dignity. In short, the consultant will only get in experience those cases that he welcomes, and this is true in all fields as much as in the question of the termination or prevention of unwanted pregnancy.

The law dates back to 1861, and, like many other laws in this country, is badly in need of reform. Professor Jeffcoate thinks that psychiatric reasons may be abused and become excuses, but there are many pregnancies which should never persist, resulting from rape, incest, or assault, or likely to result in the birth of a hopeless or useless individual, for which no legal justification for termination can be found other than the mental or emotional stress of the mother. For instance, a child of 12 was raped by a soldier in Cyprus and became pregnant ; she was 12 mentally and physically, but termination of that pregnancy would be on the face of it illegal. Our philanthropic maternity homes, run by the Salvation Army and such, have a high proportion of children under the age of consent who have become pregnant. I would not like to think that I had been a child of such a mother. Indeed, a large proportion of these children are probably unadoptable.

Scandinavian countries and many others recognize that the social and economic situation in which a potential mother finds herself has a strong bearing on the happiness of her pregnancy and the well-being of her child when born. Our juvenile courts and Borstal institutions are well inhabited by children of unfortunate mothers who are unable to exert the necessary parental care and guidance. Our magistrates have recognized this fact, and our children's officers, probation officers, N.S.P.C.C. inspectors, and staff of children's homes and babies' crèches are all fully familiar with the results of unwanted pregnancies.

The population of this country, as of the rest of the world, increases. It has been estimated that in 50 years' time it will be doubled. Surely, Sir, it is self-evident that the time has come for responsible citizens of the world to use their brains and abilities, so that by scientific control of birth rate (using contraception, abortion, and sterilization) the population of the world in posterity can be properly fed, properly housed and cared for, and in a position to live happy lives.—I am, etc.,

Newcastle upon Tyne. DOROTHEA KERSLAKE.

Mothers' Preference in Confinement

SIR,—Perhaps we may now be allowed to reply to Sir Dugald Baird's letter (February 27, p. 642), and comment on some of the points raised in this correspondence.

Mr. and Dr. Tweedie (March 19, p. 879)—and, by implication, Sir Dugald also—beg the question when they complain that we recorded the preferences of selected mothers "because they changed their place of confinement" and

disregarded the opinions of those who, by choice or from necessity, had been delivered of all their babies at home or all in hospital. We made it clear that, in our view, an investigation of this nature must be restricted to those who have actual experience of the two proffered alternatives. If a market research organization wishes to know which of two similar products is more acceptable to consumers it cautions its canvassers to eschew the opinions of those who have tried only one product. We stated in our paper that this specific investigation was directed only to mothers who had experienced both home and hospital confinement. Statistically, the 80% in favour of home confinement refers only to this group; we never said that it refers to all mothers, but we did imply that the results of this sampling warrant a rethinking of views on the whole subject. It clouds the issue even more to suppose that the mothers might not be "perfectly clear whether their preferences were to refer to their latest confinement or to their first or to some other defined [*sic*] circumstances."

We join issue with Sir Dugald Baird when he avers that, "Doctors and health visitors . . . in Ilford seem to favour home confinement, and this is presumably realized by mothers in Ilford," when he implies that we elicited these mothers' preferences by discreditable methods of interrogation, and when he seeks to devalue the answers obtained in this (or any) survey by obscuring them with supposed motivation. The health visitor, as Sir Dugald well knows, comes on the scene when the baby is 10 to 12 days old—i.e., after the domiciliary midwife has departed, or, in the case of hospital confinement, soon after the mother and her baby have returned home. In other words, she has no responsibility for the actual confinement at either place. Why, then, should she be thought to have an axe to grind? We ourselves, in our different fields, have our responsibilities for providing certain antenatal services, which are much the same for mothers to be confined in hospital as for those who elect to be delivered at home. Why should we be biased in favour of the one group or the other? We set about our survey—incidentally, long before the Cranbrook Report was published—in a completely objective manner, prompted by nothing other than curiosity to learn the facts. Having accumulated those facts, we inferred from them the self-evident conclusions. Because those inferences are, seemingly, not to Sir Dugald Baird's liking, he accuses us of having rigged the ballot.

We repudiate Sir Dugald's innuendo that doctors and health visitors cannot be entrusted with an investigation of this nature because, by their "attitude or assumed attitude" (whatever that may mean), they cannot resist investing a simple inquiry with the sinister indoctrination of a leading question. Why, too, try to explain away a mother's preference because it "may reflect [her] duties, responsibilities, and fears"? Volition is no doubt always compounded of hopes, fears, and responsibilities. Is its free and final expression to be disallowed for these reasons? We unreservedly accept Sir Dugald Baird's figures, and, even if when a mother tells him that she finds it "easier to relax at home" he chooses to qualify this by explaining that she does not really mean that she finds it easier to relax at home, we are prepared to let that pass too, provided it is clearly understood that what he is stating is his own personal—and fallible—opinion and not an ascertainable fact.

He chides us because the number of mothers (336 out of 1,552) from whom our findings were derived is too small a sample. But, if we were to limit our inquiries, for reasons already stated, to those mothers who had experience of delivery both at home and in hospital, excluding those whose views of the one or the other would be based only on hearsay, we could not increase the sample without unduly prolonging our survey; and, after all, our sample compares not unfavourably with his own (403 out of 1,938 multiparae). Both samples are, we believe, statistically valid.

We note with interest, and without comment, that Sir Dugald's findings related to parity and social class show an opposite trend to ours. The preferences of Aberdeen mothers, by all accounts, differ from those of Ilford women; they differ, too, from those expressed in Blackpool and Ealing (January 30, p. 349; March 19, p. 880). Which view represents the desires of all British women no one can say until further surveys based on samplings in other areas have been published. This is what, in our submission, the Cranbrook Committee signally failed to ascertain; or, if they did, they omitted from their report any factual corroboration of their claim that "women generally preferred to have their babies in hospital."

The fact that the hospital service can be, as Sir Dugald so rightly states—and, we would add, usually is—"efficient, humane, and reasonably convenient" is irrelevant, since we emphasized in our paper that the vast majority of the Ilford mothers who expressed a preference for home confinement did so for purely domestic reasons which cast no aspersions at all on the adequacy of hospital care. We are as anxious as Sir Dugald Baird that there should be enough hospital beds to accommodate all mothers who, for obstetric or other valid reasons, ought to have their babies in hospital. That laudable aim is not likely to be furthered if a misguided attempt is made to provide hospital beds for those who are wrongly supposed to demand them for non-medical—and even frivolous—reasons.—We are, etc.,

Barking Hospital, Essex. T. F. ELIAS-JONES.

Area Health Office, Ilford. I. GORDON.

Obesity in Childhood

SIR,—I read Dr. Philip M. Ellison's letter (March 26, p. 965) with interest, but thought it revealed a lack of perspective. Phenmetrazine is a member of the same pharmacological group as the amphetamines, but possesses only one-eighth of the central stimulating properties of these compounds, and hence a lessened tendency to the psychic sequelae referred to by Dr. Ellison. In the treatment of obesity it has almost completely replaced dextro-amphetamine sulphate. However, that it is not widely used without prescription is indicated by the fact that in the United States and Germany sale of the drug is restricted.

It would be of interest to know on what authority Dr. Ellison bases his statement that "the cycle of elevation of mood followed by depression, hallucinations, and paranoiac phenomena are very common." To my knowledge phenmetrazine has been used by a department of a London teaching hospital that deals with many cases of obesity, and a report of this work will be submitted in the near future for publication. In the hands of the medical profession this drug represents a valuable advance in the treatment of obesity, suppressing, as it does, appetite, with minimal side-effects. It would be surprising if phenmetrazine, belonging to the same pharmacological group as the amphetamines, did not exhibit similar effects in toxic doses. Connell,[1] reviewing the world literature in the light of his own experience of amphetamine psychosis, said he "would be disinclined to incriminate amphetamine as an agent in the production of a psychotic reaction in doses of less than 50 mg., unless there were biochemical evidence that the dose was in fact of this size," and this is in keeping with the reported cases

of phenmetrazine psychosis. I am unaware of any such case occurring with a dose of 75 mg. or less of phenmetrazine.—I am, etc.,

F. J. A. BATEMAN,
Director of Medical Services,
Boehringer Products Division.

REFERENCE

Connell, P. H., *Amphetamine Psychosis*, Maudsley Monograph No. 5, 1958. Chapman and Hall, London.

Shoes for Children

SIR,—The spate of correspondence in the medical and lay press which has followed the Ministry's announcement of the proposed survey on children's feet is at least an indication of the amount of interest and disquiet that the problem arouses. Dr. Margaret Emslie (April 2, p. 1052) suggests that such a survey is likely to be "fantastical and delusive," since all that is necessary is to design children's shoes properly. Perhaps she is right, but there is no proof, and it is proof that we are after. If it could be shown that there was a significant difference in the incidence of foot defects in children who had special care with their footwear as compared with a control group, and if one could demonstrate factually which types and designs of footwear were most beneficial (or least harmful), we should have a much stronger case with which to press for any necessary reforms in the care of children's feet than by the mere assertion of unproved statements, however strongly we may believe them to be true.

The word survey is perhaps misleading, as what is proposed is a long-term investigation in the course of which the effects of foot care, shoe care, and shoe design will be tested out in practice on sufficient numbers of children and over a sufficient period of time to provide statistical and factual evidence of what could, or could not, be done on a national scale, and what benefits could be expected to accrue.

In reply to Dr. Emslie, this investigation is not being financed by the shoe trade, although their technical help will certainly be needed in solving many problems in relation to shoe designs, economic considerations, and how not only to produce the right shoes but to get them on to the child's feet properly fitted.—I am, etc.,

Guy's Hospital,
London, S.E.1. T. T. STAMM.

Children's Socks

SIR,—A great many cudgels have been taken up recently in your columns on behalf of the fitting of children's shoes. May I suggest similar investigation and comment on children's socks?

Socks are manufactured in many fabrics—cotton, wool, and cotton mixtures, and man-made fibres; but a great many difficulties arise in getting the right size for any one child's feet—because one cannot try them out. The tendency to allow a child to wear slightly shrunken winter-weight socks for "just another week or two" until the weather is warm enough for new summer socks can do as much damage as badly fitting shoes. Socks bought a little too big to allow for shrinkage leave a doubled-up, uncomfortable toe and ill-fitting heel. Some socks are not finished inside and have lumpy seams at the toe which can cause corns. Good warm wool socks for the winter shrink very quickly, and even mixtures last only a few weeks with the most careful washing. Could we have a little scientific thought on this subject as well as on shoes?—I am, etc.,

Hull. CONSTANCE PHILPOTT.

Not Coincidence

SIR,—I was interested to read Dr. G. E. Honey's letter on the subject of our television programme "Emergency—Ward 10" (April 2, p. 1054). "Emergency—Ward 10" is designed mainly for entertainment and is purely fictional. Since it is based on life in a hospital we expend considerable effort in trying to produce a fair and realistic picture with a correct factual background. In fact, we employ two qualified members of the medical profession as advisers, and receive suggestions and seek further guidance from other members of the medical profession in the preparation of this programme.

Recently it was suggested to us that we might show something of the treatment of barbiturate poisoning, and at least one of the ways in which these unhappy cases occur. We decided that it would be advisable if our "patient" could be closely identified with one of the permanent fictional characters. The character of "Harry Barton" had been introduced at the beginning of February, and it was not until the beginning of March that he mistakenly took a massive overdose of barbiturates.

About this time it was brought to our notice that it would be possible to dialyse some of the barbiturate using an artificial kidney, and that the details of this treatment were contained in an article by Group Captain R. C. Jackson and Dr. Honey in the November 28 issue of your journal (p. 1134). This seemed to us an interesting and progressive type of treatment well suited to our story-line. We were advised that it would be correct and feasible to use this treatment on our now unconscious "Harry Barton." There is no mystery about how the factual and scientific side of our story followed the facts in the article. We took the view that, once having decided to introduce an artificial kidney into our story, it was best to stick exactly to the facts of a real case, so far as details of treatment were concerned.

I hope it will be realized by your readers that we do not make use of your journal as a source of inspiration for our writers, nor as a sort of home encyclopaedia from which to glean medical facts to pepper our stories. The scientific and medical background to all our stories is the subject of advice from many professional sources. In this case, the co-author of the article advised us where we might borrow the necessary scientific equipment to place on the set. The help and good will of the medical profession have been largely responsible for what success we have had, and I would venture to suggest that it is our determination to wed true medical fact to our fictional stories that has gained us the support we have received.—I am, etc.,

REX FIRKIN,
Producer,
London, W.1. Associated Television Limited.

Spiritual Healing in Hospitals

SIR,—In view of recent comments in your correspondence columns (April 9, p. 1134), it is expedient that the position of Christian Scientists *vis-à-vis* hospitals be made clear. In Section 193 of the Public Health Act, 1936, authority is provided for Christian Scientists to establish their own nursing-homes, under the title "Christian Science Houses." In these Houses, Christian Science patients are nursed with the practical wisdom necessary in a sick room; but the actual treatment they receive is by spiritual means alone, in accord "with the principles and practice of the body known as the Church of Christ, Scientist," as the Act puts it. Therefore it is rare for Christian Scientists to be in hospitals. However, if

through unusual circumstances, family pressures, or the requirements of statutory regulations a Christian Scientist has to be cared for in hospital, it is entirely orderly, specially in the latter instance, for him to have access to the ministry of his religion.

Christian Science practitioners are not connected with the National Federation of Spiritual Healers. The ethical procedure governing their relationship to hospitals was worked out quite independently with the Ministry of Health some years ago. It appears as follows in paragraph 35 of the "Legal Rights and Obligations" booklet supplied to all members of Christian Science churches in Great Britain and Ireland:

"*Ethical Procedure.*—It is agreed with the Ministry of Health that the visiting Christian Science practitioner should not set the patient against any medical treatment he may be receiving; but should the practitioner himself discern that the treatment is hampering the recovery of the patient by disturbing his religious conscience, he is then advised to take the matter up personally with the hospital authorities."

—I am, etc.,

GEITH A. PLIMMER,
Christian Science Committee on Publication.

London, W.C.2.

SIR,—Mr. Harry Edwards in his letter (April 9, p. 1135) confuses "spiritual healing treatments" with spiritual healing. Spiritual healing, which is better expressed as divine healing, is a process. "Spiritual healing treatments" indicate some sort of technique on a non-scientific basis, which is quite unacceptable to the medical profession.

Readers should refer to the letter from the staff of the Deva Hospital (March 26, p. 962), and will see some of the points expressed in the code of conduct issued by the National Federation of Spiritual Healers, which must give rise to apprehension. Mr. Edwards claims that the policy of the British Medical Association is to co-operate with spiritual healing, and that to allow accredited members of his Federation to attend the sick is putting the policy into practice. His statement is a distortion of the position.

It should be pointed out that the National Federation of Spiritual Healers, which is a spiritualistic body, is not recognized by the Churches' Council of Healing, the official liaison body between Medicine and the Churches. The C.C.H. was set up, *inter alia*, by Dr. William Temple, the late Archbishop of Canterbury, to safeguard the interests of those people who might become the victims of so-called "faith healers" and "spiritual healers." In the interests of our patients we can only deplore the introduction of "spiritual healers" to our hospitals.—I am, etc.,

HUGH H. D. SUTHERLAND,
B.M.A. Representative on the Churches' Council of Healing.

London, W.10.

Wringer Injury

SIR,—May I refer to the medical memorandum by Mr. B. Brendan Hickey and Dr. D. L. Crosby (April 16, p. 1185)? Many of the new electric wringers are, of course, fitted with automatic release devices so that the upper roller springs up when the pressure on it reaches a certain point. I have recently seen two children whose arms had been caught up to the elbow in such machines. In both cases the release device had operated and the resulting injury was only slight.—I am, etc.,

D. Y. SHARPLES.

Swindon.

Obituary

HALLIDAY G. SUTHERLAND, M.D.

Dr. Halliday Sutherland, well known for his work on the control and prevention of tuberculosis and as the author of books which appealed to a wide circle of readers, died after a short illness in the Hospital of St. John and St. Elizabeth, London, on April 19. He was 77 years of age.

Halliday Gibson Sutherland was born at Glasgow on June 24, 1882, the elder son of Dr. J. F. Sutherland, a Deputy Commissioner in Lunacy for Scotland, and received his early education at Glasgow High School and at Merchiston Castle School, Edinburgh, where he won the Walter Scott open essay prize. He studied medicine at the University of Edinburgh, graduating M.B., Ch.B. in 1906, and two years later he proceeded to the M.D., with honours. After graduation Sutherland obtained the post of bacteriologist to the Liverpool Hospital for Diseases of the Chest, where he developed his interest in tuberculin. Later he spent some time in Spain, assisting his uncle, who was the doctor in charge of a British medical clinic at Huelva. On his return to Scotland he took a post as clinical assistant at Craig House, Edinburgh, and then followed appointments at the Royal Victoria Hospital, Edinburgh, and the Westmorland Sanatorium, where he was medical superintendent, until he became medical officer to the St. Marylebone Tuberculosis Dispensary in London in 1911.

His work in London was interrupted by the first world war, in which he served first in the Royal Navy and then in the Royal Air Force. On return to civilian life Sutherland was appointed assistant physician to the Royal Chest Hospital and physician to St. Marylebone Hospital, and then, in 1920, he became Deputy Commissioner of Medical Services (Tuberculosis) for South-Western England and Wales, a position he held until 1925. For the next 15 years he was an assistant medical officer under the London County Council until, in 1941, he was appointed assistant medical officer of health for Coventry. Two years later he moved to Birmingham to become executive medical officer for mass radiography in the city, and he was medical director of the mass radiography centre there from 1948 to 1951, being employed also as a consultant in the National Health Service. He was honorary physician to, and a member of the council of, the Queen Alexandra Sanatorium Fund, and a past-president of the Tuberculosis Society of Great Britain.

Halliday Sutherland was a tenacious fighter for the principles he thought were right, whether medical or political. Many of his views were contentious, but there was no doubt about his sincerity. In 1945 he stood, unsuccessfully, as the Labour candidate for Parliament for the Scottish Universities, and in his address he attacked things done by "monopolists, rings, cartels, and vested interests at the cost of human happiness."

During his professional life he wrote many articles and several books about tuberculosis, including *Pulmonary Tuberculosis in General Practice* (1916) and *Tuberculin Handbook* (1936), but his great success as an author began with an autobiography entitled *The Arches of the Years*. Published in 1932, it ran to 35 English editions and was also translated into eight European languages. Other books

followed quickly: *A Time to Keep* (1934), *Laws of Life* (1935), *In My Path* (1936), *Lapland Journey* (1938), *Hebridean Journey* (1939), *Southward Journey* (1942), *Control of Life* (1944), *Spanish Journey* (1948), and *Irish Journey* (1956). He also wrote the introduction to *Religio Medici* in the Everyman Series, and edited, in 1943, the 45th edition of his father's handbook on *First Aid to the Injured and Sick*.

With his religion, as in other matters, he was not afraid of controversy, and he successfully defended (eventually in the House of Lords) an action for libel brought against him by Dr. Marie Stopes. In 1954 he was appointed Knight Commander of the Order of Isabel the Catholic, and he was presented with the Pope John XXI Medal in 1955.

Halliday Sutherland married Miss Muriel Fitzpatrick in 1920 and had five sons (one of whom was killed in the second world war) and one daughter.

Dr. HARLEY WILLIAMS writes: Halliday Gibson Sutherland was described by his great opponent, Dr. Marie Stopes, whom he finally defeated in the House of Lords after a series of libel hearings, as "the most cocksure man in the British Empire." This jibe did not do full justice to the many resources of wit and courage of a man who packed three careers into his 77 years. He was a pioneer in tuberculosis, a religious controversialist, and a best-selling author.

In his undergraduate days in Edinburgh he had been a pillar of the Liberal faith, and indeed was more temperamentally fitted for law and politics than medicine. After graduating he become Dr. Robert Philip's favourite pupil, and edited (1911) a book of papers on the newly born tuberculosis movement, written by Philip's pupils and friends. The book found its way into the hands of the Prime Minister, Mr. Asquith. As a consequence, Dr. Philip became Sir Robert, with Sutherland as his Grand Vizier. He was abounding in original ideas. He produced the first health-education cinema film made in this country, and as tuberculosis officer for Marylebone he started the first open-air school in the bandstand of Regent's Park.

After the first world war his friendship with Philip cooled, and about the same time Sutherland joined the Catholic Church. He now emerged in a new role, as a controversialist over artificial contraception, which he opposed on genetic and religious grounds. Those polemics are now past history, but they did have the effect of adding to the English law of libel. In 1933 appeared Sutherland's best book, *The Arches of the Years*, the title borrowed from the Catholic poet Francis Thompson. Sutherland had the gift of exhibiting his own adventures and misadventures with engaging modesty, combined with self-assurance. This book was followed by several other volumes of travel biography, in the same attractive idiosyncrasy.

Sutherland was a red-haired, blue-eyed, Highland Scot, with an up-tilted nose. He made friends and enemies with equal readiness. Both will remember this entertaining and cantankerous man who opened several new paths and gave to the world the full flavour of his personality.

MORTON MARKS, M.R.C.S., L.R.C.P., D.L.O.

Mr. Morton Marks, consultant ear, nose, and throat surgeon to Mile End and St. Leonard's Hospitals, London, died on April 22, at the age of 41.

Morton Marks was educated at St. Paul's School and qualified from Guy's Hospital in 1943. After doing medical, surgical, and E.N.T. house appointments, he took the D.L.O. in 1945 and then joined the R.A.F.V.R., serving as squadron leader and E.N.T. specialist in Egypt. On demobilization he was appointed registrar at the Royal National Throat, Nose, and Ear Hospital and first assistant to the E.N.T. department at St. George's Hospital and the Victoria Hospital for Children, Tite Street.

At the Royal National Throat, Nose, and Ear Hospital he came to the notice of the late Mr. Lionel Colledge, under whom he worked for several years and whose influence and teaching guided his particular interest in diseases of the larynx, a subject to which he always gave special interest. In otology, too, his gentle dexterity produced a greater proportion of dry mastoid cavities and preservation of hearing than many could claim, since he always performed the wide meatal flap which was characteristic of Lionel Colledge's surgery. In 1950 he was appointed consultant E.N.T. surgeon to both Mile End Hospital and St. Leonard's Hospital.

One of Morton Marks's greatest characteristics was his boundless energy. No day was long enough for his work: no out-patient session or operating-list too large, yet each patient received his unhastening attention. No work was ever skimped, and with all this he was always in good humour. Nothing ever seemed to upset his constant gay equanimity which made him so popular with his colleagues and the nursing staff of the hospitals he visited.

Apart from his hospital work and an extensive practice, no request for help from other hospitals was ever refused, and how he managed to do such a prodigious amount of work so effortlessly and efficiently was a constant source of admiration. In addition he made time to devote himself to the more academic side of his specialty. He was a regular attender at the Royal Society of Medicine, and was often to be found at other hospitals familiarizing himself with some new technique. He also found time to contribute articles to various journals, including a paper on tonsillectomy in children published in this journal.

Thus fate has robbed us at such an early age of one whose untiring energy and diligence had earned for him great esteem and whose friendly charm had gained him so many real friends. Up to two months ago, when it was evident that he was mortally ill, some innate desire for activity stimulated him to continue his work, and, though morphine was often necessary to dull the pain, even that could not blunt his energy. It was not until his physical strength failed completely that he was forced to give up. After that his one constant thought was to get back to work. He was a devoted family man and was also a delightful and friendly host to his large circle of friends.

Mr. Marks leaves a widow and a daughter and a son.—E. F. S.

HUMPHREY ENGLAND, M.R.C.S., L.R.C.P.

Dr. H. England, who formerly practised at Chesham Bois, Bucks, died on April 13, aged 92.

Humphrey England was born at Winchester on August 11, 1867, the second son of William England, M.D.Ed., a leading practitioner in Winchester for many years. Educated at Gonville and Caius College, Cambridge, and St. Thomas's Hospital, Humphrey England qualified in 1897 and after holding several resident hospital appointments practised in West Kensington. In 1910 he moved to Chesham Bois, Bucks. In this growing centre he soon acquired both patients and friends. He built his own house, "The Four Winds," where he and his wife dispensed a gracious hospitality for many years.

When the first world war came, England at once volunteered. He was rejected at first as being over military age, but in 1916 his persistence was rewarded by a captain's commission in the R.A.M.C. He served in France for the rest of the war, and after the armistice he was in charge of a hospital ship conveying sick and wounded Turkish prisoners-of-war to Constantinople.

Soon after his demobilization he was appointed part-time medical officer of health and school medical officer for the rural district council of Amersham. England was too conscientious a man to give partial service to important and increasing responsibilities. Keenly interested in public health, it absorbed more and more of his working days; and, gradually relinquishing private practice, he held these

appointments with success up to the age of 79. He drove a car up to the age of 80. In his last years he was crippled with osteoarthritis, but his mental energy and interest in art, literature, and people were unabated.

He married Miss Mary Douglas Stephenson, formerly a sister at Charing Cross Hospital, in 1903. They had one daughter. Mrs. England died on March 5, 1959. Dr. England's declining years were spent at Braunton, in Devonshire, and he died in hospital at Barnstaple at the ripe age of 92.—A. S. MacN.

JOHN DOCKRAY, M.B., F.R.C.P.

The obituary of Dr. John Dockray was published in the *Journal* of March 12 (p. 810).

Mr. DOUGLAS JACKMAN, formerly vice-chairman of the South-West Metropolitan Regional Hospital Board, writes: The tributes paid to John Dockray are well deserved, but may a layman who has enjoyed his friendship speak of the tremendous contribution he made to the affairs of the South-West Metropolitan Regional Hospital Board and later the new Wessex Region? It was a great privilege to share his confidence, for he was the friend of all with whom he came into contact. In our committees his influence was outstanding. I remember so well when he told me that, as we were making more use of him than he thought we should when first he joined us, he thought it necessary that his sessions should be reduced. It was typical of the man—great in every sense. A fine Christian gentleman, courteous to everyone, humble yet brilliantly efficient. Every lay member of the Board who came into contact with him, or of our staff in Winchester, had absolute trust in him, and the countless deeds of kindness, done in secret, without fuss or bother, will live long in our hearts. He was our "beloved physician," and the closing words of Thomas Hardy, the Wessex novelist, in *The Woodlanders*, ". . . for you was a good man, and did good things," are a fitting epitaph.

JESSIE E. WRAITH, M.B., B.S., D.M.R.E.

Dr. Jessie E. Wraith (née Sheret), who was consultant radiologist to a number of hospitals in and near Manchester, died on March 29. She was 64 years of age.

Jessie Evelyne Sheret was born on February 11, 1896, and studied medicine at the University of Durham, graduating M.B., B.S. in 1922. She decided early on to specialize in radiology, and she took the D.M.R.E. of Cambridge in 1923, and not long afterwards she was appointed radiologist to the Ancoats Hospital, Manchester, and the Manchester Babies Hospital. Over the next few years she steadily built up the reputation she soon established in her specialty, and she was co-author of papers on such subjects as cholecystography and massive pulmonary collapse. Her fame spread beyond Manchester, and she was appointed radiologist to the Westmorland County Hospital, Kendal, to the Ethel Hedley Hospital, Windermere, and to the Westmorland Sanatorium. After the establishment of the National Health Service she became consultant radiologist to the hospitals in the north and mid-west groups of the Manchester Regional Hospital Board.

She married Dr. F. Wraith, of Lymm, Cheshire, early in her career, and he survives her, together with a son and daughter of the marriage.

Sir HARRY PLATT writes: Dr. Jessie Wraith gave ten years' devoted service to the Ancoats Hospital at a time when the department of radiology, under the direction of Dr. E. W. Twining, was emerging from the restricted accommodation in which that great pioneer Dr. Alfred Barclay had established the first unit of its kind in Manchester. Those were the days of long working hours and casual protection from the hazards of irradiation. In such circumstances Dr. Jessie Wraith worked cheerfully and unobtrusively, admired and respected by all who came into contact with her. She carried these same qualities to the hospitals whose staff she joined in later years; and so a multitude will cherish her memory.

W. R. FORRESTER WOOD, M.B., B.Ch., F.R.C.S.

The obituary of Mr. Forrester Wood was published in the *Journal* of April 23 (p. 1281).

J. H. C. writes: I knew Bill Forrester Wood since 1924, but it was only in latter years I really got to know him well as the most worthwhile man I have ever known. He was so calm, so considerate, so wise in his judgments, and above all so kind in the troubles of others, so very courageous in his own. He was a magnificent surgeon, a magnificent man. We shall miss him more than I can say.

Medico-Legal

CULPABLE NEGLECT OF TELEPHONE

[FROM OUR LEGAL CORRESPONDENT]

The medical practitioner's telephone is a vital part of his practice which he cannot afford to neglect. In some circumstances neglect to keep the telephone covered for messages may result in legal liability. These circumstances arose in the case of Corder *v.* Banks (*The Times*, April 9), where Mr. James Matthew Banks, a plastic surgeon practising from Harley Street, was sued by Mrs. Stella Rachel Gresham (formerly Miss Corder). Mr. Justice McNair delivered a reserved judgment on April 8.

Plastic Operation on Face

In 1952 the plaintiff consulted Mr. Banks concerning a condition below her eyes. Mr. Banks at first advised an operation for the removal of excess fat from under the plaintiff's eyelids at a fee of 50 guineas in addition to nursing-home charges: but on considering the plaintiff's means he agreed to do the operation at a reduced fee of 10 guineas under a local anaesthetic with the plaintiff attending as an out-patient only. The court held that although this latter course involved increased risk, no charge of professional negligence could be made out on the grounds of Mr. Banks's failure to insist on nursing-home treatment. The criticism of Mr. Banks concerned not his performance of the operation, but the aftercare. Bleeding might occur during the first 48 hours after the operation, and if it were not properly attended to irreparable damage might result. The court held that if a patient was allowed to go home after an operation, proper directions should be given to him, and the surgeon, or a properly qualified substitute, should remain available to deal with any emergencies. Moreover, if the surgeon was relying upon the telephone as a means whereby the patient could inform him of any emergencies, it was essential that the telephone should be adequately covered so that messages should be received and transmitted to the surgeon.

Message Not Received

An emergency did arise in the form of substantial bleeding from the stitches within the first 48 hours. Proper directions had been given to the patient regarding action in such emergency, and there was no suggestion that Mr. Banks was not in fact available to deal with it. However, although proper notification of the bleeding was sent to the address given by Mr. Banks, it was not received by him, owing either to his failure to keep his telephone adequately covered or to the failure of those for whom he was responsible to inform him of the message. That failure amounted to professional negligence. The court was satisfied that as a result of that negligence the plaintiff's face had been disfigured since 1952 (when she was 29). In respect of that disfigurement general damages of £1,500 were awarded.

This case is, of course, of importance to the general practitioner as well as to the specialist, despite the fact that the general practitioner is rarely able to employ anyone full-time to answer his telephone. If a patient is directed to inform his doctor of certain developments in the course of treatment, the doctor must ensure that the method directed for the transmission of messages will be effective. If a reliable watch cannot be kept on the telephone, some other means of communication must be devised.

PARENT'S REFUSAL OF CONSENT

[FROM OUR LEGAL CORRESPONDENT]

On March 29, in Melbourne, Australia, Alvin Leonard Jehu, a Jehovah's Witness, was found guilty of manslaughter of his baby daughter (*The Guardian*, March 30). Jehu had refused to consent to a blood transfusion for his daughter, although it might have saved her life. The jury made a recommendation for mercy, and Jehu was bound over for five years in the sum of £100.

The jury added a rider to their verdict (which the State Attorney-General promised to consider) calling for legislation to enable hospital authorities to give treatment to save life irrespective of parents' wishes.

CORONERS' CASES

Patient Electrocuted in Operating Theatre

A faulty cardiac monitoring machine was responsible for the death of a patient on the operating table in the London Chest Hospital on March 22. Mr. Edward Edgar, aged 62, was about to have an operation for the removal of an air cyst in his right lung when he received a fatal electric shock. The shock occurred when the cardiac monitor was connected with the main electricity supply.

The anaesthetist, Dr. R. N. G. Atherstone, connected the sensing head of the monitor to the patient's left thumb with adhesive tape. A diathermy earthing plate was attached to the right leg. The lead from the sensing head was plugged in and the machine began to work on its batteries. Shortly afterwards the mains supply was switched on and the patient was observed to move slightly. This is not unusual under light anaesthesia. Because the cable was in the way the mains plug was removed to correct this and then reinserted, whereupon the same movement was noticed in the patient. Dr. P. H. Dennison, who was assisting Dr. Atherstone, received an electric shock at the same time as the patient moved, and it was then obvious that something was wrong. An electrical fault was suspected, and immediate orders were given to disconnect all electrical equipment from the patient. Meanwhile the patient was rigid and had stopped breathing; he soon became pulseless. 100% oxygen was administered and a paralysing dose of tubocurarine given. Cardiac massage, intracardiac adrenaline, and repeated defibrillation by another machine were all unsuccessful. Resuscitation was abandoned after one hour.

The machine was acquired in May of last year. It had had to be returned to the makers on at least two occasions for repairs. It had been tested by Dr. Atherstone on the morning of the operation, but only on the batteries. Without expert knowledge and special equipment it would not have been possible for him to have tested it otherwise. Mr. A. Wells, an electrical engineer, said in evidence that the machine's case had no earth and there was a broken wire inside. The absence of the earth was, in his opinion, a fault. The resultant effect of the faults was that when the machine was switched on the normal mains current increased to 330 volts and was delivered to the sensing head. With the diathermy pad providing an earth the patient was electrocuted. The coroner, Dr. R. I. Milne, remarked that the machine seemed to be very vulnerable to injury although its design was not at fault. Exonerating Dr. Atherstone from all blame, the coroner recorded a verdict of accidental death due to electrocution (*The Times*, April 5).

Medical Notes in Parliament

POPULATION STATISTICS

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Not content with a debate on April 8 on a private member's motion calling for improved facilities within the N.H.S. for research into the treatment of renal diseases, Members of the Commons tackled two other medical topics before their Easter recess: rheumatism in Western Scotland (April 13) and educational standards for mental nurses (April 14). In addition, on April 12, the Population (Statistics) Bill completed its passage through the Commons. It now only awaits the assent of the Lords to the changes the Commons have made in it.

Reporting on Stillbirths

Chief among these changes is a new clause (Additional matters to be included in annual reports of Registrar-General and Registrar General for Scotland), introduced by the MINISTER OF HEALTH. Its effect is (*a*) to put on a proper statutory footing the reporting to Parliament annually of the statistics derived under the procedure of the Population (Statistics) Act, 1938 (for which hitherto there has been no statutory requirement, although the information has habitually been given); and (*b*) to achieve the reporting of information about stillbirths, as expanded by Clause 2 of the Bill.

This expansion of the basis of statistical information, and the reporting of it, Mr. D. WALKER-SMITH told the House, would help research and subsequent genetic evaluation. In Scotland the cause of death in stillbirths was already recorded, but the numbers were insufficient for research purposes. It was expected that in England and Wales about 3,800 stillbirths and 3,400 deaths after birth would be available each year for the study of congenital malformation. With the Scottish figures this would give a total of about 8,200 cases a year. With these figures it was hoped in due time that it would be possible to determine the proportions and types of congenital abnormalities and genetic defects. It would then be possible to go further and investigate what factors were responsible for producing these genetic defects, and to find the proportion of cases due to the working of defects long present in the race compared with those due to newly arisen genetic change. Time was required for that evaluation to be possible. In Part 3 of the annual review, entitled "Commentary," would be the comment, explanation, review of trends, and so on of the new information authorized by the Bill.

In summary, said the Minister, they were concerned with four matters. There was the broadening of the base of statistical information; the promulgation of this new information, thus spreading further light on the genetic structure of the population; the research by the Medical Research Council on the basis of that; and further evaluation by the Council in the light of the results of its research. The Registrars-General would be able to do the promulgation and the commentary in the annual reports under the new clause. The Medical Research Council would be assisted in its research both by the broadened statistical information and by the commentary, and would be able to make its further evaluation in the light of them. All in all, this would be a valuable addition.

Anxiety about Effects of Radiation

Dr. EDITH SUMMERSKILL (Warrington, Lab.) accepted the new clause in lieu of one she had proposed calling for an annual report by the Minister on the information gained from the information obtained under the Bill, although she had some reservations on whether the Minister's clause went far enough. One thing which hung over the whole world to-day, she said, was fear of the effects of nuclear radiation on the health, morbidity, and mortality of the population.

She had wanted the Minister to say the Medical Research Council would produce an annual report on the subject. It might make an encouraging report, saying that the strontium rate had been reduced and therefore the apprehensions aroused the previous year could be dismissed. And she indicated plainly to the Minister that when his first annual report appeared the Opposition would want to debate it.

Mr. WALKER-SMITH explained that the commentary in Part 3 of the Registrar-General's annual review would be made by persons of medical as well as statistical skill. These reports, based on the statistical parts of the review, would be valuable apart from anything produced by the Medical Research Council. The Council, although it would not be reporting on an annual basis, would continue to present the results of its research as and when it was useful and possible to do so. He also said that, in addition to what was being done under the new clause, he was considering whether through the Chief Medical Officer he could provide any more information on this general range of topics in the Ministry of Health report.

October 1 for New Information

Another change that has been made is to bring into operation the new requirements for information about stillbirths on October 1. The Minister preferred this date to July 1, which had been suggested, because of the necessity for adequate consultation with the medical profession on the appropriate form of certificate to be used. The Schedule was also amended to enable information to be obtained at the registration of a birth of the number of previous children who were stillborn, as well as the number born alive.

CRIME AND PUNISHMENT

Statistics of Murder

The EARL OF SELBORNE sought from the Government on April 6 figures of the number of murders in a comparable period before and after the passing of the Homicide Act. The Act came into force on March 21, 1957. In the first 12 months after that, he was informed, 151 murders became known to the police in England and Wales, and in the second 12 months 127—a total of 278. In the corresponding periods before the Act was passed there were 129 in 1955–6 and 146 in 1956–7—a total of 275. (These figures exclude cases originally recorded as murders but later found not to be murder.) The figures for the periods before and after the passing of the Act are not strictly comparable, EARL BATHURST, the Home Office spokesman, explained, because the Act changed the definition of murder. The principal change was the introduction of the special defence of diminished responsibility. There were 31 cases in 1957–8 and 20 in 1958–9 in respect of which persons charged with murder were then found guilty of manslaughter after pleading diminished responsibility. Most of these would probably have been regarded as murder before the Homicide Act was passed.

Capital and Corporal Punishment

Sir THOMAS MOORE (Ayr, Con.) asked the Home Secretary on April 14 if, in view of the fact that 78% of the population was now in favour of the restoration of corporal punishment for crimes of violence against the person and 74% in favour of capital punishment for all types of murder, he would reconsider his policy on crime and punishment. Mr. BUTLER said he had seen a variety of analyses of the figures on which Sir T. Moore based his statements about the opinion of the population of the United Kingdom on these complex and difficult subjects. He would not be prepared to propose a further change in the law relating to capital punishment until sufficient time had elapsed to enable the effect of the Homicide Act, 1957, to be assessed. He had referred the question of corporal punishment to the Advisory Council on the Treatment of Offenders, and was awaiting their report.

Sir THOMAS MOORE: But surely the Home Secretary feels that the will of the majority must prevail. Otherwise government might as well be handed over to the Opposition, and God forbid that that should happen. Mr. BUTLER: We have to mix the mixture a little between a poll of this sort, in which the answers are very varied—some of the conclusions were very different from what some M.P.s think—with the ordinary democratic process by which we are elected. I am quite ready to study the former and be guided by the latter, but on matters like this we must introduce some small degree of science, and that is what I am attempting to do.

Imprisonment of Children

A Bill to restrict the committal to prison of children under 16 years of age, and to provide for the transfer to remand homes or remand centres of certain children who have been so committed, was introduced in the House of Commons on April 6 and given a formal first reading. Mr. ALAN BROWN (Tottenham, Lab.) found no opposition when he sought leave to bring in this Bill. Society had received a severe shock three weeks before, he said, when it came to light that a schoolgirl of 14 was imprisoned in Holloway Gaol, and serious public concern had been expressed at the disclosure.

He subsequently visited the Governor of Holloway, who told him she was completely opposed to children being sent to prison. At Wormwood Scrubs on March 22 he discovered nine boys below school-leaving age imprisoned there. What was termed the "boys'" prison contained those aged 14 to 21. There was a real danger of the possible criminal indoctrination of schoolboys by the older youths of the "young adult" class. The knowledge that criminal statistics revealed an alarming increase in crime, to an extent that was near to placing the over-17 but under-21 group in a class by themselves, was perturbing. The Governor of Wormwood Scrubs, the two assistant governors, and the chief prison officer were unanimous in their condemnation of sending schoolboys to such prisons.

Where Else to Send Them?

The argument that if the children were released from prison there was nowhere else to send them might be true to some extent but should not be accepted as wholly true. If the shortage of remand homes was to be pleaded, why had so many been closed? Between January, 1951, and December, 1954, 18 local-authority remand homes, containing 495 places, were closed. Since 1955 six voluntary-organization homes had been closed, and nine others owned by local authorities. On the credit side, six new ones had been opened and one was being built—a net loss of eight. The figures for 1958 showed 484 boys and 12 girls of school age had the stigma of prison attached to them; at the moment he thought 120 to 150 were in prison. The children's service had become the Cinderella of the social services.

QUESTIONS IN THE COMMONS

Government Spending Dissected

Sir A. HURD (Newbury, Con.) asked the Chancellor of the Exchequer on April 13 if he would show in shillings and pence the breakdown into main items of each £1 of Government spending as estimated for the current financial year. Sir EDWARD BOYLE, Financial Secretary to the Treasury, gave the following figures:

	s.	d.
National debt	2	3
Defence	5	5
Health services	2	1
Personal payments	1	11
Agricultural support		10
Assistance to local services	3	1
Other services and payments	3	5
Surplus	1	0
	£1	0 0

Removing Doctors' Cars

Mr. J. CRONIN, F.R.C.S. (Loughborough, Lab.), asked the Home Secretary what instructions had been given to the Metropolitan Police as to the procedure they should adopt when they found parked, in a central London street in which there was no specific prohibition of parking, a car bearing the official badge of the British Medical Association, not causing obvious obstruction or any potential danger; and how these instructions were modified if the car had displayed a near-by address at which the driver could be contacted.

Mr. BUTLER stated that the relevant regulations empowered the police to remove cars from the roads when they were causing danger or when they were causing obstruction by interfering with the passage of other vehicles near a road junction or by being parked so far from the edge of the carriageway, or so near another vehicle, as unduly to restrict the space available for the passage of other vehicles. Cars left by doctors in these circumstances were liable to be removed. He was informed by the Commissioner of Police that where a car displayed the special badge issued by the British Medical Association for this purpose, with a note of the address at which the owner might be found, it was not normally removed without reference to the owner unless speedy removal was considered to be essential because the car was causing danger or very serious obstruction.

Causes and Effects of Noise

The names of the members of the committee "to examine the nature, sources, and effects of the problem of noise, and to advise what further measures can be taken to mitigate it," were announced on April 13. The chairman is Mr. A. H. Wilson, F.R.S. (deputy chairman, Courtaulds, Ltd.); the deputy chairman Professor T. Ferguson Rodger (professor of psychological medicine, Glasgow University); and the members Dr. Albert Fogg (director, Motor Industry Research Association), Dr. F. B. Greatrex (manager, Rolls-Royce Ltd.), Sir Arnold Hall, F.R.S. (technical director, Hawker-Siddeley Group), Mr. N. Longley (James Longley & Co.), Dr. R. C. M. Pearson (medical officer of health, Newcastle upon Tyne), Mr. L. H. A. Pilkington (director of Pilkington Brothers), Sir Julian Pode (managing director, Steel Company of Wales), Professor E. J. Richards (professor of aeronautical engineering, Southampton University), Miss M. R. Tabor (housing manager, Stevenage New Town), Mr. T. J. Urwin (town clerk, Bristol), and Mrs. E. Webley (member of Women's Voluntary Service in South Wales).

Vital Statistics

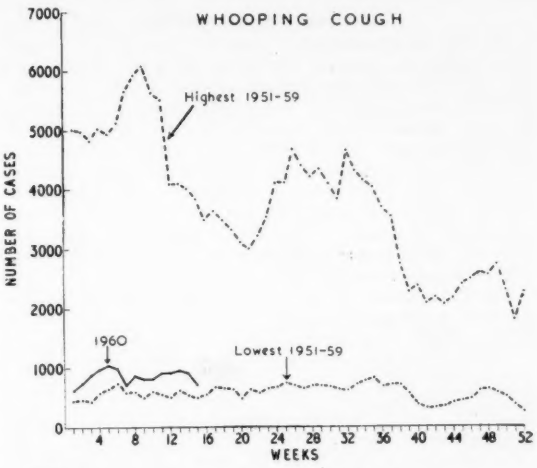
Deaths from Tuberculosis and Cancer in 1959

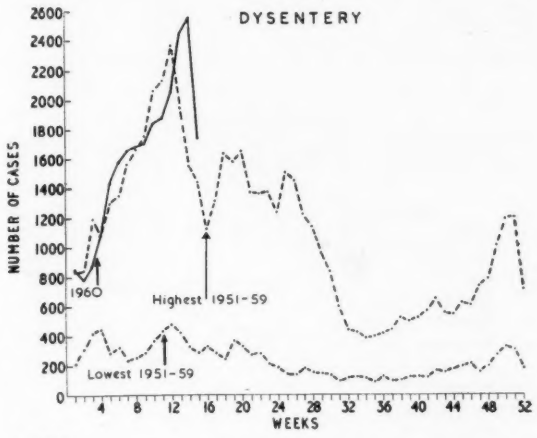
In 1959 3,475 people died from respiratory tuberculosis (against 3,999 in 1958). Since 1949 the death rate from respiratory tuberculosis has fallen by over 80%.

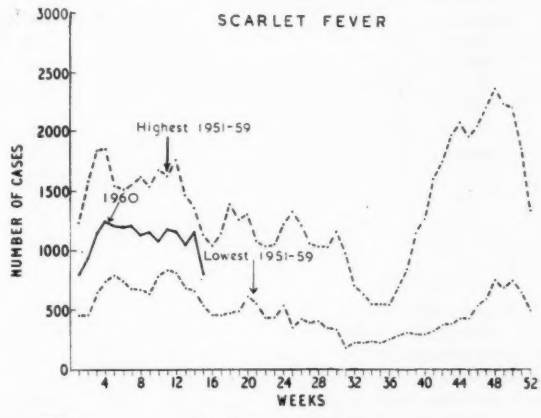
The death rate for all forms of cancer was slightly lower for men and slightly higher for women in 1959 than in 1958; but the rate for cancer of the lung and bronchus increased in men from 784 to 831 and in women from 119 to 123 per million population. 35% of the 51,783 male deaths from cancer were certified as due to cancer of the lung and bronchus, whereas only 6% of 45,333 deaths from cancer in women were ascribed to this cause.—*Registrar-General's Weekly Return*, No. 13, 1960.

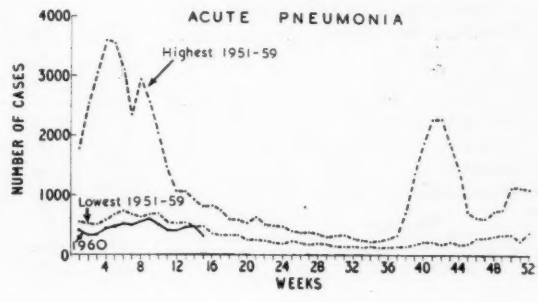
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases in 1960

During the first quarter of 1960 the notifications of acute poliomyelitis in England and Wales were the lowest since the disease assumed epidemic proportions in 1947. Dysentery reached a new high level, the notifications exceeding those recorded in the first quarter of 1956. The notifications of paratyphoid and typhoid fevers, pneumonia, meningococcal infections, and measles were lower than in the first quarters of recent years. The incidence of diphtheria has, apparently, become fairly stationary: during the quarter three areas accounted for half of the total notifications—Plymouth C.B. 9, London 8, Walthamstow M.B. 7. The mortality from influenza was relatively light.

The Table shows the uncorrected notifications for the first quarters of the past five years.

	1956	1957	1958	1959	1960
Scarlet fever	11,400	10,315	10,735	15,198	14,512
Whooping-cough	16,870	38,251	7,442	7,989	11,236
Measles	35,164	233,826	49,359	271,651	23,466
Acute poliomyelitis	366	516	292	217	84
Diphtheria	89	59	39	44	45
Meningococcal infections	436	385	389	384	278
Dysentery	19,297	13,594	13,861	13,618	19,857
Pneumonia	12,905	8,491	11,351	17,744	5,900
Paratyphoid and typhoid fever	98	94	75	193	57
Deaths from influenza	2,104	361	2,093	7,098	504

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending April 9	Week Ending April 16
Dysentery		
Cheshire	107	**91**
Macclesfield M.B.	4	**52**
Essex	281	**202**
Southend-on-Sea C.B.	4	**15**
West Ham C.B.	34	**18**
Braintree and Bocking U.D.	0	**13**
Chigwell U.D.	48	**41**
Romford M.B.	86	**56**
Gloucestershire	39	**41**
Bristol C.B.	26	**34**
Lancashire	430	**333**
Bolton C.B.	18	**29**
Liverpool C.B.	50	**54**
Manchester C.B.	33	**34**
Oldham C.B.	41	**32**
Worsley U.D.	8	**15**
London	271	**222**
Bermondsey	61	**36**
Islington	42	**28**
Lambeth	16	**24**
Southwark	35	**23**
Norfolk	94	**70**
Norwich C.B.	53	**40**
Warwickshire	34	**35**
Birmingham C.B.	16	**19**
Coventry C.B.	7	**12**
Wiltshire	51	**33**
Swindon M.B.	28	**19**
Cricklade and Wootton Bassett R.D.	14	**11**
Yorkshire West Riding	313	**160**
Bradford C.B.	81	**29**
Leeds C.B.	38	**11**
Sheffield C.B.	48	**62**
Glamorganshire	31	**31**
Ogmore and Garw U.D.	16	**16**
Glasgow	134	**81**
Dunbarton County	0	**21**
Measles		
Dorsetshire	89	**146**
Sturminster R.D.	14	**72**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 9** (No. 14) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	3	0	0	1		2	0	4	0	
Dysentery	2,535	271	215	24	10	906	122	129	10	6
Encephalitis, acute	3	1	0	0		2	0		0	
Enteric fever:										
Typhoid	0	0	0	0		0	0	0	0	
Paratyphoid	3	0	0	1		22	13	1 (B)	0	
Food-poisoning	229	45	10			366	37	19	11	
Infective enteritis or diarrhoea under 2 years				12	35				13	26
Measles*	2,143	70	70	5	21	22,811	1376	598	437	380
Meningococcal infection	24	1	7	1	1	20	4	12	0	5
Ophthalmia neonatorum	25	4	4	0		31	0	5	0	
Pneumonia†	465	21	190	3	5	692	33	228	41	28
Poliomyelitis, acute:										
Paralytic	2	0	0	0	1	14	2	0	1	
Non-paralytic	0	0	0			5	0	0		
Puerperal fever§	192	38	7	1		222	32	15	0	
Scarlet fever	1,169	43	55	35	15	689	48	55	28	26
Tuberculosis:										
Respiratory	465	49	83	10		685	68	80	20	
Non-respiratory	39	5	8	2		54	4	14	0	
Whooping-cough	916	84	230	3	31	634	23	42	60	118

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	3	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	0	1	0	2	0	3	0	0
Influenza	36	2	1	0	0	206	3	10	7	13
Measles	0	0	0	0	0		1	1	0	
Meningococcal infection		0	0				1	1		
Pneumonia	669	39	27	14	7	746	50	27		27
Poliomyelitis, acute	0	0		0	0	2	0		0	0
Scarlet fever	0	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	79	4	3	4	1	81	6	6	0	7
Non-respiratory			0	1	2		1	0	0	1
Whooping-cough	1	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	367	25	24	4	11	314	30	37	10	14
Deaths (excluding stillbirths)	11,158	894	642	163	179	10,703	788	660	187	246
LIVE BIRTHS	15,958	1298	1099	319	361	15,867	1309	992	300	376
STILLBIRTHS	327	27	24			346	21	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

North Middlesex Hospital

The new out-patient department at the North Middlesex Hospital was opened on April 26 by Her Royal Highness Princess MARGARET.

As long ago as 1934 Middlesex County Council considered plans for rebuilding the entire hospital, and demolition on the site had been started when war broke out. A bombing raid in 1944 resulted in the loss of 350 beds, together with the whole of the out-patient, casualty, receiving, and radiographic departments. The hospital was transferred to the Regional Board in 1948, and the planning of a new out-patient department was begun. The new building marks the second stage of the ultimate rebuilding of the hospital. It is a four-story block with its main axis running east and west and a two-story block on the north side. It includes a urological department, five general-purpose clinics, a dental unit, a pharmacy, a pathological laboratory and radiographic department, as well as a hydrotherapy pool, gymnasiums, an electrically screened room for electromyograph equipment and a department for electrocardiography and clinical photography.

Mental Nursing

The views of a representative group of mental and mental-deficiency nurses—brought together by the ward and departmental sisters' section of the Royal College of Nursing to consider the impact of the Mental Health Act on the care of mental patients both in and out of hospital—have been summarized in a recently published memorandum (*A Comprehensive Mental Nursing Service*, The Royal College of Nursing, price 2s. 6d.).

Among their many recommendations are that psychopathic patients should be accommodated in special units; that old people and long-stay patients should not be isolated and allowed to "degenerate into little communities of forgotten individuals"; and that, to avoid wasting time and money, it is just as important that there should be a minimum educational standard for the mental nurse as for the general one.

Synthetic Detergents

The *Third Progress Report of the Standing Technical Committee on Synthetic Detergents* (H.M.S.O., price 1s. 6d. net) says that there has been no pronounced change during 1959 in the concentration of these detergents at various testing points, with the exception of a marked reduction in the River Lea—one of the sources of London's water supply. Moreover, these substances do not appear to affect the treatment of sewage in septic tanks.

Foaming, however, is still a problem, and a large-scale trial of a new basic material which might reduce it was begun at Luton in August, 1958. The experiment continues, but so far the results indicate that the new material is an improvement on the old.

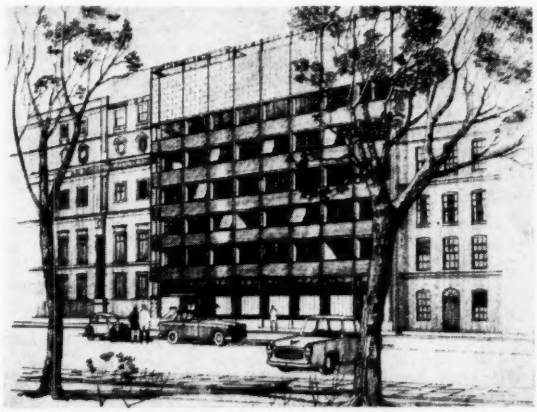
Queen's Honorary Surgeons

Professor JOHN BRUCE has been appointed an honorary surgeon to the Queen in Scotland. Professor Sir JAMES LEARMONTH, who has resigned this post, has been appointed extra surgeon to the Queen.

Imperial Cancer Research Fund

"Inevitably all our hopes and ambitions hinge on finance," said the honorary treasurer of the Imperial Cancer Research Fund, Mr. A. DICKSON WRIGHT, at the Fund's annual general meeting on April 21. The laboratories which are now being built, designed in Cornish granite, red brick, and black bronze round an open courtyard, will cost at least £1m. to build, a further £250,000 to equip and staff, and about £500,000 a year to support and maintain. A drawing of them is shown here, and it is hoped they will be completed by June, 1961.

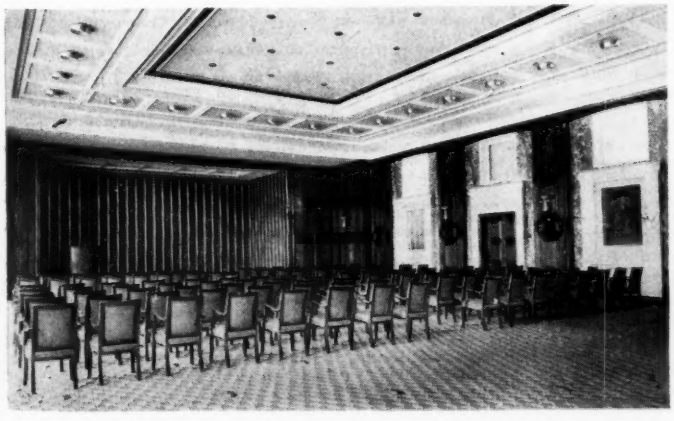
Sir CECIL WAKELEY, chairman of the Fund's Council, spoke about the important work done by the Fund's workers and referred to in the *Annual Report*, 1958-9, on the treatment of



breast cancer in women and on viral aetiology of cancer. The Fund's research laboratories are now reorganized on the basis of four divisions: two at Lincoln's Inn Fields—of chemistry and biochemistry and of pathology—and two at Mill Hill—of experimental biology and virology and of physiology and endocrinology. Work in the laboratories at the moment is concentrated on a relatively small number of major groups of closely related research projects which, as they demand the skills of more than one discipline, have been planned on an interdivisional basis. The groups may be classified under the headings of the tumour-inducing properties of viruses, the endocrinological aspects of cancer; the leukaemias, and the biological properties of tumour cells—the first and second absorbing the greater number of the Fund's research workers. Plans are now being drawn up for a considerable extension of research into the leukaemias in man and in experimental animals.

Toxic Chemicals in Agriculture

The Research Study Group on Toxic Chemicals in Agriculture is prepared to receive written evidence on this subject from persons or organizations. It should be addressed to the secretary of the Group, Dr. E. J. MILLER, Plant Pathology Laboratory, Hatching Green, Harpenden, Herts.



Royal College of Obstetricians

On July 13 the QUEEN will open the new premises of the Royal College of Obstetricians and Gynaecologists in Sussex Place, Regent's Park. The cost of the completed building has amounted to £400,000, of which £125,000 was given by the Nuffield Provincial Hospitals Trust, £30,000 by the Wellcome Trust, and £10,000 by the Simon Marks Trust. Over £30,000 was contributed by Fellows and Members of the College. A further £500,000 is needed as an endowment fund. The photograph shows the impressive Nuffield Assembly Hall, panelled in African walnut and marble. The windows overlook the Regent's Park lake. (Photograph by Central Press Photos, Ltd.)

Nuffield Foundation Grant to Zoo

The Nuffield Foundation has made a grant of £100,000 to the Zoological Society of London to found an Institute of Comparative Medicine and to provide two Senior Research Fellowships. A committee of medical and veterinary specialists under the chairmanship of Sir ROY CAMERON, with a planning group under the chairmanship of Professor G. PAYLING WRIGHT, has been appointed to advise the Society's council on the Institute's organization.

Granada Research Chair in Communication

Dr. D. MACKAY, reader in physics at London University, has been appointed to the research chair in communication endowed by Granada T.V. Network which has been established at the University College of North Staffordshire.

He has said (*The Times*, April 21) that he will be chiefly concerned with the ways in which information is represented and "processed" in the brain as well as with the theory of brain-like self-organizing systems, natural and artificial.

Institute of Criminology, Cambridge

Dr. D. J. WEST, formerly psychiatric registrar at the Maudsley Hospital, London, has been appointed an assistant director of research at the Institute of Criminology, Cambridge, for three years from January 1, 1960. (*Cambridge University Reporter*, March 25.)

The Ford Foundation has made a grant of £23,000 to the Institute of Criminology, Cambridge University. It will finance American experts who will join in the Institute's training and research programme. (*The Times*, April 20.)

Family Doctor

The May issue of *Family Doctor* is now available at a cost of 1s. 6d. It includes articles on hay-fever by Dr. K. C. HUTCHIN, on boxing by Dr. J. A. WAYCOTT and Mr. J. H. DOGGART, and on cancer of the breast by Sir CECIL WAKELEY.

People in the News

Sir MILTON MARGAI, the premier of Sierra Leone, who qualified in medicine at the University of Durham in 1926, is in London for constitutional talks on the future of his country.

Dr. R. J. A. BERRY, late professor of anatomy and dean of the faculty of medicine, Melbourne University, has been awarded an emeritus professorship by the University Council.

COMING EVENTS

Institute of Dermatology.—Exhibition: Dr. E. J. MOYNAHAN, "Paediatric Dermatology," May 2–25, St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London, W.C.2.

"Eye on Research."—Dr. M. F. PERUTZ, F.R.S., and Dr. J. C. KENDREW, F.R.S., with filmed contribution by Professor J. D. BERNAL, F.R.S.; "Shapes of Life," B.B.C. T.V.: May 3, 9.15 p.m.

Royal College of Surgeons of England.—Lecture and demonstration (colour television): "Cell, Chromosome, and Virus Microscopy in Cancer Research." Principal speakers: Professor G. J. CUNNINGHAM, Professor P. C. KOLLER, and Dr. R. J. C. HARRIS. To be held at the College, May 10, 5.45 p.m. Details and tickets from Mr. W. F. DAVIS, at the College, Lincoln's Inn Fields, London, W.C.2.

Institute of Urology.—Week-end course: "Medical Aspects of Urology," May 13–15. Details from the secretary, Institute of Urology, 10, Henrietta Street, London, W.C.2.

British Society for Immunology.—Spring meeting, May 21, 22, The London Hospital Medical College's Hall, Ashfield Street, London, E.1. Opening symposium: "Immunological Aspects of Diseases of Connective Tissue." Details from Dr. R. G. WHITE, Bacteriology Department, The London Hospital, London, E.1.

B.B.C. Radio.—Tribute to the late Sir ARCHIBALD MCINDOE, May 5, Home Service, 10.15 p.m.

Faculty of Radiologists.—Postgraduate week-end course: "Diagnostic Radiology and Radiotherapy," May 21, 22. Details from the Secretary of the Faculty, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

Association of Physicians of East Africa.—Annual conference, June 23–25. B.M.A. members wishing to attend will be welcome and should notify the Hon. Organizing Secretary, P.O. Box 6811, Nairobi, Kenya.

University of Clermont-Ferrand.—Institut d'Hydrologie et de Climatologie: International Summer Course, July 15–30. A few scholarships in the form of free accommodation and meals are offered to students of medicine or of pharmacy. Details from Monsieur le Directeur des Cours de Vacances, Institut d'Hydrologie et de Climatologie, Faculté de Médecine et de Pharmacie, Boulevard Gergovia, Clermont-Ferrand (Puy-de-Dôme), France.

NEW ISSUES

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.*1.

BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY.—Issued quarterly (£4 4s. annually). The new issue (Vol. 15, No. 1) includes:

British Pharmacological Society: Winter Meeting, 1960.
The Accumulation of Isoniazid in Tissues, and the Course of Experimental Tuberculosis. J. Venulet, Krystyna Jakimowska, M. Janowiec, and Alicja Urbanska.
The Effect of Substance P on the Superior Cervical Ganglion of the Cat. D. Beleslin, B. Radmanović, and V. Varagić.
The Pharmacological Actions of (*m*-Hydroxyphenethyl)trimethylammonium (Leptodactyline). V. Erspamer and A. Glässer.
Reciprocal Potentiating Action of Depolarizing Drugs on the Isolated Frog Rectus Abdominis Muscle. J. H. Fleisher, J. P. Corrigan, and J. W. Howard.
Assay of Lysergic Acid Diethylamide and its Passage from Blood into the Perfused Cerebral Ventricles. M. Draškoci.
The Effect of Iproniazid and Imipramine on the Blood Platelet 5-Hydroxytryptamine Level in Man. Elizabeth F. Marshall, G. S. Stirling, A. C. Tait, and A. Todrick.
Oxidation of 5-Hydroxytryptamine and Related Compounds by Mytilus Gill Plates. H. Blaschko and A. S. Milton.
The Effect of Precursors of Noradrenaline on the Response to Tyramine and Sympathetic Stimulation. J. H. Burn and M. J. Rand.
Sympathetic Postganglionic Cholinergic Fibres. J. H. Burn and M. J. Rand.
Anoxia and Ventricular Fibrillation; with a Summary of Evidence on the Cause of Fibrillation. J. H. Burn and S. Huković.
The Neuromuscular Blocking Properties of a Series of Bis-quaternary Tropeines. C. G. Haining, R. G. Johnston, and J. M. Smith.
Inhibition of Mast Cell Disruption and Histamine Release in Rat Anaphylaxis in Vitro. Comparison with Compound 48/80. I. Mota and Tisue Ishii.
The Mode of Neuromuscular Blocking Action of Chlorpromazine. C. Su and C. Y. Lee.
The Quantitative Assay of Corticotrophin using Rats Treated with Hydrocortisone Acetate. J. B. Dekanski and Margaret I. Harvie.
The Structure-activity Relationships of the Antiviral Chemotherapeutic Activity of Isatin β-Thiosemicarbazone. D. J. Bauer and P. W. Sadler.
Pharmacological Properties of Thalidomide (α-Phthalimido Glutarimide), a New Sedative Hypnotic Drug. G. F. Somers.
The Action of Sympathetic Blocking Agents on Isolated and Innervated Atria and Vessels. S. Huković.
Action of Two Ethyl Thiol Esters Against Experimental Tuberculosis in the Guinea-pig. G. E. Davies and G. W. Driver.
The Effects of Ambucetamide on Human Myometrial and Other Preparations, and its Antagonism to the Menstrual Stimulant. V. R. Pickles and H. J. Clitheroe.
A Study of Antagonists of 5-Hydroxytryptamine and Catechol Amines on the Rat's Blood Pressure. A. S. Outschoorn and J. Jacob.
The 5-Hydroxytryptamine Content of Mouse Brain and Whole Mice after Treatment with some Drugs Affecting the Central Nervous System. A. L. Bartlet.
Ganglion-blocking Properties of Atropine-like Drugs. J. G. Bainbridge and D. M. Brown.
Pharmacologically Active Peptides in the Blood and Urine of Animals Infected with Babesia rodhaini and Other Pathogenic Organisms. L. G. Goodwin and W. H. G. Richards.
Metabolism and Excretion of Di(*p*-Aminophenyl) Sulphoxide in Different Animal Species. A. A. Levi and G. A. Snow.
Depletion of Pituitary Corticotrophin by Reserpine and by a Nitrogen Mustard. M. Saffran and Marthe Vogt.
The Effects of Intracisternal Sarin and Pyridine-2-aldoxime Methyl Methanesulphonate in Anaesthetized Dogs. R. V. Brown.
Effects of Reserpine, Chlorpromazine and Sodium Salicylate on the Enzymic Activity of Rat Liver. S. M. Kirpekar and J. J. Lewis.
A Comparison of the Kallikrein-kinin System in Sheep and Dogs. J. H. Gaddum and P. S. Guth.
Unspecific Drug Action. The Effects of a Homologous Series of Primary Alcohols. H. P. Rang.
The Action of Local Anaesthetics on the Spinal Cord of the Cat. D. Taverner.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

ARCHIVES OF DISEASE IN CHILDHOOD.—Issued bi-monthly (£4 4s. annually). The new issue (Vol. 35, No. 179) includes:

Abdominal Tumours in Infants and Children. C. Everett Koop.
Ovarian Neoplasms in Children. Isabella Forshall.
Primary Tumours of the Liver in Infants and Children. H. William Clatworthy, Jr., E. Thomas Boles, Jr., and William A. Newton.
Results with Abdominal Resection in Hirschsprung's Disease. F. Rehbein and H. von Zimmermann.
A New Operation for the Treatment of Hirschsprung's Disease. Bernard Duhamel.
Intestinal Obstruction in the Newborn Infant. M. Grob.
Simultaneous Intra- and Extrapulmonary Sequestration. V. Kafka and V. Beco.
Pulmonary Sequestration. P. Talalak.
Hiatus Hernia in Childhood. J. H. Johnston.
Temperature Changes during Neonatal Surgery. Malcolm H. Gough.
Incubator for Infants Undergoing Surgery. P. P. Rickham and Jean M. Jenkins.
Developmental Posterior Enteric Remnants and Spinal Malformations. J. F. R. Bentley and J. R. Smith.
Accessory Enteric Formations. J. R. Smith.
Total Colectomy and Ileo-anal Anastomosis in the Treatment of Ulcerative Colitis in Children. Tyge Cl. Gertz.
Surgical Aspects of Patent Ductus Arteriosus. B. J. Bickford.
Vesico-intestinal Fissure. P. P. Rickham.
Le Mesurier's Operation for Hare Lip. A. Oberniedermayr.
Clinical Manifestations of Primary Hyperoxaluria. E. G. Hall, E. F. Scowen, and R. W. E. Watts.

BRITISH HEART JOURNAL.—Issued quarterly (£3 annually). The new issue (Vol. 22, No. 2) includes:

The Human Pacemaker and its Pathology. Reginald E. B. Hudson.
Myocardial Injury from Therapeutic Irradiation. Mary Catterall and William Evans.
Electrocardiographic Changes in the First Week of Life. K. K. Datey and P. E. Bharucha.
Left Ventricular Aneurysm in the African. A. O. Lurie.
Myxoma of the Left Atrium. Harold E. Aldridge and William F. Greenwood.
Spectrophotometric Micro-estimation of Blood Oxygen Saturation. F. E. Weale.
The Vectorcardiogram and Electrocardiogram in Ventricular Septal Defect. J. Beregovich, S. Bleifer, E. Donoso, and A. Grishman.
Prednisolone Maintenance Therapy in Chronic Pulmonary Heart Disease. J. N. Mickerson.
Electrocardiographic Signs of Left Ventricular Hypertrophy and Strain in Hypertensive Patients. F. O. Simpson.
Familial Heart Disease with Skeletal Malformations. Mary Holt and Samuel Oram.
Incidence of Congenital Heart Disease in Singapore. C. S. Muir.
The Ventilatory Response to Carbon Dioxide in Mitral Disease. H. G. Pauli, F. E. Noe, and E. O. Coates.
Status Anginosus. Cornelio Papp and K. Shirley Smith.
Electrocardiographic Changes in Atrial Septal Defect following Surgical Correction. D. Hywel Davies, Ray Pryor, and S. Gilbert Blount, Jr.
Deterioration after Mitral Valvotomy. Charles Baker and W. E. Hancock.
Total Anomalous Drainage of Pulmonary Veins into the Left Gastric Vein. K. M. Laurence and R. J. K. Brown.
Proceedings of the British Cardiac Society.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 2

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., special university lecture in pathology by Professor A. A. Liebow (Yale): Birth and Growth of Collateral Vessels.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. L. R. West: Echinococcosis.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor P. K. Duraiswami: Experimental Causation of Congenital Defects.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Professor Z. M. Bacq (Liége): Enzymatic Inactivation of Adrenaline and Noradrenaline.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School.—5 p.m., First Almroth Wright Lecture by Professor A. St. G. Huggett, F.R.S.: Foetus as an Anaerobe: Some Prenatal Problems.

Tuesday, May 3

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. J. Wallace: Vascular Anomalies in the Lower Limbs.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Professor K. J. Zülch (Cologne): Recent Work on Cerebral and Spinal Infarction.
LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., special university lecture in dentistry by Professor E. Husted (Copenhagen): Ameloblastoma.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. J. R. B. Williams: Polymyositis.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Professor J. K. Russell: Megaloblastic Anaemia of Pregnancy.

Wednesday, May 4

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Dr. F. Avery Jones: Observations on Prognosis in Alimentary Disease.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Fungi as Saprophytes and Pathogens.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald: Pulmonary Changes in the Reticuloses.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. R. E. B. Hudson: Human Pacemaker and its Pathology.
ROYAL FREE HOSPITAL.—5.15 p.m., Dr. W. V. McDermott, Jnr. (Boston): Hepatic Coma.

Thursday, May 5

ABERDEEN UNIVERSITY: DEPARTMENT OF SURGERY.—At Medical School, Foresterhill, 5 p.m., Professor R. B. Welbourn: Hypophysectomy in Advanced Breast Carcinoma.
DUBLIN UNIVERSITY: TRINITY COLLEGE.—At Anatomy Theatre, 5 p.m., Montgomery Lecture in Ophthalmology by Professor Hans Goldmann (Berne): Diagnostic Value of the Biomicroscopy of the Posterior Parts of the Eye.
HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor P. R. Allison: Swallowing and Dysphagia.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. H. T. Howat: Diagnosis and Treatment of Pancreatic Disease.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Otolaryngology Lecture by Sir Victor Negus: Air-conditioning in the Nose.
ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Physiology Department, Queen's College, Small's Wynd, Dundee, 5 p.m., Professor T. Ferguson Rodger: Neuropharmacological Approach to Psychiatry.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration by Dr. M. Partridge: Psychiatry.

Friday, May 6

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. J. Wallace: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. L. Livingstone: clinical demonstration.
INSTITUTE OF NEUROLOGY.—4.30 p.m., Dr. J. P. Martin: Observations on Muscular Rigidity and its Relation to the Functions of the Basal Ganglia.
MEDICAL ELECTRONICS DISCUSSION GROUP.—At Institution of Electrical Engineers, Savoy Place, W.C., 5.30 for 6 p.m., discussion to be opened by Mr. W. J. Perkins: Methods of Recording Measurements—Digital or Analogue.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Dr. Deborah Doniach: Some Ancillary Diagnostic Methods in Thyroid Disease.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—3.30 p.m., Dr. A. Rae Gilchrist: Cardiac Patient as a Surgical Problem.

Saturday, May 7

FACULTY OF ANAESTHETISTS: ROYAL COLLEGE OF SURGEONS OF ENGLAND.—10.30 a.m., scientific meeting. Subject: Hypoxia. Papers by Professor E. A. Pask, Squadron Leader J. Ernsting, Dr. J. B. Brierley, and Dr. P. D. Bedford and B. R. J. Simpson. 4 p.m., panel discussion.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—12 noon, Professor S. Podvinic (Belgrade): Upper Respiratory Pathology in Asthma.
KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Maidstone Technical School for Girls, Albion Place, Maidstone, 3 p.m., Dr. A. D. B. Clarke: Uses and Abuses of the I.Q. Test.

Sunday, May 8

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., clinical discussion for general practitioners. Seminar by Mr. Maxwell Ellis: Common Ear, Nose, and Throat Conditions.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Conley.—On April 12, 1960, to Lorna, wife of Neil Conley, M.B., Ch.B., 32, Eldon Grove, West Hartlepool, Co. Durham, a daughter.
Jones.—On April 16, 1960, at St. David's Hospital, Bangor, Caern., to Mary, wife of Dr. Ellis Jones, a sister for William and David—Catherine Charlotte.
Osmond.—On April 12, 1960, at Southmead Hospital, Bristol, to Anne (formerly Welsh) and Dr. D. G. Osmond, a son—Roger Gordon.
Page.—On April 11, 1960, to Marian (formerly Cox) and Dr. Tim Page, of Craufurd House, Maidenhead, Berks, a son.
Penney.—On March 12, 1960, at Bishop's Castle, Salop, to Belinda (formerly Rudd), wife of Dr. G. St John Penney, a brother for Adrian and Oliver.

MARRIAGES

Craig—Raine.—On June 23, 1960, at St. Nicholas Church of England, Kenilworth, Dr. William S. R. Craig, of Halifax, Yorks, to Dr. Kathleen W. Raine.

DEATHS

Bilderbeck.—On April 5, 1960, Alured Charles Lowther O'Shee Bilderbeck, M.B., B.S., D.P.H., D.T.M., colonel, I.M.S., retired, of Columbwood, Richmond Avenue, Bexhill, Sussex.
Coulthard.—On March 29, 1960, at Oakfield Farm, Crockham Hill, near Edenbridge, Kent, Joseph Jefferson Coulthard, M.B., F.R.C.S.Ed.
Czajkowski.—On May 15, 1959, Pawel Czajkowski, M.D.
Gunewardene.—On April 3, 1960, Theodore Hamnet Gunewardene, M.R.C.S., L.R.C.P.
Harneis.—On April 1, 1960, at "In The Ray" Nursing Home, Maidenhead, Berks, Theophilus William Morcom Harneis, M.R.C.S., L.R.C.P., of Urchfont, Wilts, aged 86.
Hessel.—On April 3, 1960, at Tanshelf Lodge, Pontefract, Yorks, William Thomas Hessel, M.B., Ch.B., aged 77.
Irvine.—On March 25, 1960, in Northern Rhodesia, Colin William Gardner Irvine, M.B., Ch.B., D.P.H., D.T.M.&H., late of 28, Park Road, Rosyth, Fife.
Jamison.—On March 27, 1960, Samuel Wallace Jamison, M.B., B.Ch., of Church Street, Portstewart, Co. Londonderry.
McVail.—On April 3, 1960, at Worthing, Sussex, Elizabeth Maud McVail, M.D., D.P.H., late of St. John's Wood, London, N.W.
O'Donoghue.—On April 2, 1960, Daniel Francis O'Donoghue, M.B., B.Ch., of 14, Gibson Square, London, N.
Roe.—On April 5, 1960, at St. Luke's Hospital, Richard William Ely Roe, L.R.C.P.&S.I. & L.M.
Stalker.—On April 4, 1960, William Fleming Stalker, M.B., Ch.B., of 58, Castle Road, Scarborough, Yorks, aged 63.
Tibbles.—On April 4, 1960, at The White House, Albany Street, London, N.W., Sydney Granville Tibbles, L.R.C.P.&S.Ed., L.R.F.P.S., late of Harley Street, London, W.
Wilson.—On April 4, 1960, at Cumbria, Dartmouth Road, Paignton, Devon, William Etherington Wilson, F.R.C.S., aged 66.
Wraith.—On March 29, 1960, Jessie Evelyne Wraith (formerly Sheret), M.B., B.S., D.M.R.E., of Brookfield, Lymm, Cheshire.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Blood for Emergency Transfusion

Q.—*When an immediate replacement transfusion is needed for obstetric haemorrhage, is it preferable to give blood of the patient's own group, but not cross-matched, or group O Rh-negative blood?*

A.—There is always some risk in giving blood which has not been cross-matched, and this risk is, of course, increased in a woman who has undergone a pregnancy. Therefore it is most desirable to make a cross-matching test of some kind and to keep the patient going meanwhile with an infusion of plasma or a plasma substitute, such as dextran. If it is thought that blood must be given immediately to save the patient's life, then on the whole it is safer to give O Rh-negative blood. One must assume that, if there is no time to cross-match blood, there is also no time to determine the patient's ABO and Rh group by careful procedures.

Ocular Effects of Ultra-violet Light

Q.—*What is the effect on the eyes of manufacturing operatives who are indirectly exposed to ultra-violet light, the source of which is shaded from direct view? The nature of their work prevents the operatives from wearing coloured glasses. Are there any colourless glasses which would be of use?*

A.—Ultra-violet light is absorbed by the superficial ocular structures (the cornea and conjunctiva) and does not penetrate further into the eye. The average minimum exposure required to produce symptoms has been reported to be about 150 foot-candle-minutes measured in terms of visible light.[1] Repeated exposures are cumulative. It is unlikely that such intensities of ultra-violet light reach the eyes of the operatives concerned in the question, but a mild chronic blepharoconjunctivitis and increased sensitivity to light might occur after prolonged exposure. Ordinary spectacles of plain glass would absorb most of the ultra-violet light under such conditions. Crookes's "A glass" is efficient and has little effect on other visible wavelengths.

REFERENCE

[1] Kinsey, V. E., Cogan, D. G., and Dinker, P., *J. Amer. med. Ass.*, 1943. **123**, 403.

Carbon-paper Dermatitis

Q.—*Are there any dermatological hazards from frequent contact with carbon paper?*

A.—Contact dermatitis due to handling carbon paper is sometimes suspected in young women who work as typists. One would expect such sensitivity to be due to epidermal allergy, and this should be easy to confirm by patch-testing. It is generally supposed that epidermal allergy may arise in respect of almost every substance with which the skin may come in contact. However, allergic sensitivity to carbon paper seems to be very uncommon.

Failure to Ejaculate

Q.—*A young man of 24 appears perfectly normal in every respect. Libido and orgasms are normal, but he has never had an emission of semen. Why is this?*

A.—The most likely cause of failure of ejaculation, in spite of the normal occurrence of orgasm, is retrograde ejaculation into the bladder. In this, because of incoordination of the sphincter mechanism of the neck of the bladder, the semen passes into the bladder instead of distally along the urethra. Diagnosis depends upon finding spermatozoa in the urine voided after orgasm. The cause is obscure and treatment is ineffective, though occasionally pregnancies have resulted from artificial insemination of spermatozoa recovered by centrifuging the urine voided after coitus. There is no reason to suppose that testosterone injections would be of any benefit.

Failure of ejaculation, in spite of normal erectile potency, may be of psychogenic origin, but in this case there is nearly always failure of orgasm also.

Differential Diagnosis in Amoebiasis

Q.—*What are the diet and treatment for chronic intestinal amoebiasis when the stools are negative for E. histolytica cysts, although ulceration of the bowel and abdominal tenderness persist?*

A.—The answer to this question hinges on the diagnosis. Persistent ulceration of the bowel—in contrast to ulceration lasting for only a few days after treatment—in the absence of *Entamoeba histolytica* or its cysts in the stools is more likely to result from ulcerative colitis or schistosomiasis than from an amoebic infection. If stool examination continues to show no evidence of an amoebic infection the diagnosis should be dropped, for ulceration due to *E. histolytica* can invariably be relied upon to heal after standard treatment.

The question of diet in this case does not therefore arise, since, after proper diagnosis and treatment of amoebic ulceration, the ulcers heal. It may be stated that in general the diet for those undergoing treatment for amoebic dysentery should be light, be low in its content of roughage, and be free from spices, alcohol, and other gastro-intestinal irritants.

NOTES AND COMMENTS

Smoking and Migraine.—DR. JANET M. GILLISON (Ayr) writes: The answer under "Smoking and Migraine ("Any Questions ?" February 20, p. 579) interests me enormously. The expert writes: "Perhaps migraine is due to a lack of noradrenaline in chromaffin stores in the brain." Is there any published writing expounding this theory ? If so, I should be very interested to have the reference. If it is a tentative suggestion, then is any research being done on these lines ? This theory seems to me to fit in with the ideas of the aetiology of migraine that come to me from long observations on myself and others.

OUR EXPERT replies: There is as yet no published writing expounding the theory, and it is nothing more than a tentative suggestion. However, research is being planned, and if the suggestion has a basis in fact it should be possible to establish it without great delay.

Correction.—We regret two errors in our report of the symposium on adrenergic mechanisms (April 16, p. 1201). It was Otto Loewi (*not* Loewe) who "established the theory of chemical transmission firmly"; and Langley's initials were J. N., *not* H. H.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).

Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volume 3 (8s. 3d.).

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